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## ORIGINAL ARTICLES

# PRELIMINARY OBSERVATIONS ON THE CULTIVATION AND MORPHOLOGY OF A MICROORGANISM FROM THE CEREBROSPINAL FLUID OF PATIENTS WITH MULTIPLE SCLEROSIS

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Of the many theories concerning the nature of multiple sclerosis, the possibility of a spirochetal etiology has the most interesting and controversial history. In 1904, Borst[8] and in 1911 Buzzard[10] commented on the similarities between central nervous system syphilis and multiple sclerosis and postulated a spirochetal etiology for the latter. In 1917, Kuhn and Steiner[28] described a spirochete in the blood and tissues of guinea pigs and rabbits inoculated with spinal fluid and serum of patients with multiple sclerosis. Subsequently, using special histological techniques, Steiner repeatedly demonstrated the same organism, which he named *Spirochaeta myelophthora*, in the brain and spinal cord of patients with this disease [29,43-46].

Both confirmation (Adams, Blacklock and McCluskie[1], Austregesilo and Borges Fortes[3], Blackman[7], Buscher[9], Kalberlah[26], Marinesco[30], Pettit[32], Rogers[34], Scheinker[36], Schuster[37], Siemerling[38], Speer[42]) and denial (Birley and Dudgeon[6], Collins and Noguchi[12], Hassin and Diamond[21], Stevenson[47]) of these findings were forthcoming in the succeeding 20 years. Except for the observations of Steiner, there has been little support for the spirochetal nature of multiple sclerosis in this country, although there has

been more enthusiasm in Europe, particularly on the part of Ahrens[2] and Simons[39,40,41].

Further impetus to the problem was added by Ichelson in 1957 when she reported successful cultivation of a spirochete from the spinal fluid of 59 of 76 patients with multiple sclerosis[23]. No growth was obtained in 28 control patients. In the same year Simons using new direct histological techniques demonstrated the presence of spirochetes in the spinal fluid as well as in the brain of patients with multiple sclerosis[40,41]. More recently Needham, Voss and Daly at the Mayo Clinic failed to isolate *Spirochaeta myelophthora* from the cerebrospinal fluid of 32 patients with multiple sclerosis[31].

This report is concerned with our experiences with the cultivation of a microörganism from the cerebrospinal fluid of patients with this disease using the technique described by Ichelson.

**Materials and Methods.** Observations on 34 patients are included in this report. The clinical diagnosis in each case was established on the basis of the history, the course of the disease and repeated neurological examinations by several observers. Thirteen patients had multiple sclerosis. We believe the evidence is sufficient to establish a definite diagnosis in 10 cases, a probable diagnosis in one, and a possible diagnosis in the remaining 2. The 21 control patients were hospitalized patients most of whom had other diseases of the central nervous system (Tables 1 and 2). During the course of the study the diagnosis in each case was unknown to those reading the cultures.

In a preliminary study, culture medium prepared by Ichelson was inoculated with the spinal fluid of 11 patients, 4 of whom had multiple sclerosis. Following the encouraging results obtained in this series (Table 1), culture medium was prepared in our own laboratory, inoculated with spinal fluid and observed for growth.

PREPARATION OF MEDIUM. The medium contains the following ingredients[23,25]:

| | |
|---|---|
| Brewers' Thioglycollate Medium (Difco—0236–01)* | 20 gm. |
| Bacto Asparagine (Difco) | 0.4 gm. |
| L. Cystine (Difco) | 0.2 gm. |
| Peptone (Witte's) | 1.0 gm. |
| Distilled Water (Commercial Purock or Sunbeam) | 1000 ml. |

This mixture is gently brought to the boiling point until all ingredients are in solution, then cooled to 37° C. and kept at this temperature. The following are then added:

| | |
|---|---|
| Rabbit Sera | 20.0 ml. |
| Human Sera (Fresh, Serologically Negative) | 60.0 ml. |

*Ichelson recommends the use of this specific lot.

The medium is sterilized in the following manner: With the use of a vacuum pump, the solution is passed through a fine glass sintered filter to minimize the possibility of clogging the sterilized Selas filter. The filtrate is poured into a 2 liter graduated cylinder, and a previously sterilized 03 Selas filter approximately 10" long is inverted and placed in the cylinder. With the aid of the vacuum pump the medium is filtered into a sterile vacuum flask. During the entire procedure, the temperature is maintained at 37° C. by keeping the graduate in a 37° C. water bath. At this point, the medium should have a clear amber color. If the medium has absorbed too much oxygen during the procedure, it will be green or amber-green and should not be used.

The medium is dispensed in 6 to 8 ml. aliquots into previously sterilized 16 × 125 mm. cotton and gauze stoppered tubes. The tubes are flamed, charring the excess cotton, and further sealed by inserting previously sterilized, size "O" rubber stoppers. Tubes can be stored several weeks in the refrigerator in this condition. After several days of refrigerated storage, the tubes should demonstrate a very slight agar haze extending 1/3 to 1/2 of the broth level. This should not be confused with contamination. Prior to inoculation with samples of spinal fluid, all tubes were incubated for 48 to 72 hours at 37° C. to test for sterility.

INOCULATION OF MEDIUM. Cerebrospinal fluid is collected by lumbar puncture using sterile technique. The cell count and protein content of each fluid were determined and the colloidal gold curve, Kolmer test for syphilis, sugar and chloride were done in most instances. Electrophoretic studies were

not performed on the cerebrospinal fluids. Approximately 10 ml. of cerebrospinal fluid in a sterile test tube were immediately sent to the laboratory and centrifuged for 2 hours at 1500 rpm. All but 1.0 to 1.5 ml. of the centrifuged sample was decanted, and the remainder transferred aseptically in 0.5 ml. aliquots to a tube of the above described medium.

To maintain anaerobiasis during incubation, approximately 5.0 ml. of a previously sterilized and cooled solution of equal parts of paraffin oil and yellow vaseline was aseptically introduced into each tube. The paraffin oil and vaseline mixture had been sterilized in a dry heat oven for 3 hours at 170° C. Immediately prior to use the mixture was autoclaved for one hour at 20 lbs. and allowed to cool.

All inoculated tubes were incubated at 28 to 30° C. Blind transfers to the same medium were made on all tubes at approximately the third week, at the end of 2 months and every month thereafter. Cultures were made of uninoculated medium and uninoculated medium plus the paraffin and vaseline mixture.

EXAMINATION FOR GROWTH. Each culture tube was examined every 2 to 3 weeks. Preparations for examination were made as thin as possible. Phase microscopy (97× objective, 15× wide-field oculars) was superior to dark field illumination particularly in the identification of early forms of the organism.

Growth in positive cultures is usually first noted in about 3 weeks. At this time approximately one or two organisms per 10 fields are observed. The early forms appear as small spherical bodies that may have a small tail-like structure. Observation and identification of these early forms is extremely difficult as they may resemble artefacts. The electron microscope is of value in this early identification. It usually takes at least 3 months for the organism to attain maturity. The mature organisms, as observed in a wet mount with the phase microscope, appear as slender, flexuous bodies varying in length from approximately one to 50 micra, averaging 7 micra. The usual form is that of a spiral with at least one complete turn. However, slender rod-shaped cells with or without terminal or sub-terminal dense spherical bodies (gemmae) were observed. In addition, a number of slender rods with flexures of varying degrees, as well as the previously described early forms were seen. Occasionally, highly refractile bodies were observed in the slender rod-shaped organisms.

Motility usually consists of a slow rotation about the long axis, resulting in slow linear motion. Violent lashing as well as a "pinwheel" type motion have been observed. The latter motion, which occurs primarily with the slender filamentous organisms, is believed to result in the formation of tightly curled structures. The earlier forms appear to lack true motility. The organism is readily stained with Giemsa and Fontana[16] stains, but does not stain with the usual aniline dyes nor with the Sudan stains or Alcian blue. When stained by the Fontana method, the organisms appear shorter, thicker and with more convolutions.

Examination of formaldehyde fixed unshadowed preparations with the electron microscope demonstrate the organism to be free of any axial filaments or flagellae. A slight but definite spiral ridge was noted in several organisms. The only prominent protoplasmic pattern was a number of small electron-scattering bodies, which may correspond to the highly refractile bodies observed under phase microscopy. The gemmae appear as protuberances of the filamentous structures. They are occasionally surrounded by a delicate membrane-like capsule and have no definable internal structure. Figures 1 to 15 illustrate the varying morphology of the organism.

**Results.** Using the medium prepared by Ichelson, mature growth was obtained in 2 of 4 patients with multiple sclerosis (Table 1). All 4 were considered typical moderate to far-advanced cases. No growth was obtained in the 7 control patients nor from uninoculated Ichelson medium.

Using our own medium, positive cultures were obtained in 3 patients with typical multiple sclerosis (Table 2). In 2 patients with the typical disease, the cultures were considered suspicious during the initial periods of observation in that it was thought that early forms were present. In none of these, however, have these organisms shown any further development beyond this stage. Negative cultures were obtained in one definite case, one probable case and 2 possible cases of multiple sclerosis as well as in the 14 control patients and in uninoculated medium.

TABLE 1.—CLINICAL AND LABORATORY DATA ON MULTIPLE SCLEROSIS AND CONTROL PATIENTS IN WHOM CEREBROSPINAL FLUID CULTURES WERE DONE USING ICHELSON MEDIUM

| | | | | | *Cerebrospinal Fluid* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Pt.* | *Age* | *Sex* | *Race* | *Diagnosis* | *Cells c. mm.* | *Protein mg. per 100 ml.* | *Sugar mg. per 100 ml.* | *Chlorides mg. per 100 ml.* | *Kolmer* | *Colloidal Gold* | *Culture* | *Remarks* |
| 1. F.H. | 27 | M | W | Multiple Sclerosis 6 Years | 3 wbc's | 47 | | | Neg. | 0(10) | Neg. | Advanced multiple sclerosis; prominent pyramidal tract signs. Bitemporal disc pallor. |
| 2. H.L. | 38 | M | W | Multiple Sclerosis 12 Years | 0 | 49 | | | Neg. | 0112321100 | Suspicious Early forms seen | Bedridden typical far advanced case. Prominent cerebellar and pyramidal tract signs. |
| 3. J.T. | 36 | M | W | Multiple Sclerosis 12 Years | 0 | 38 | | | Neg. | 0(10) | Pos. | Bitemporal disc pallor; bil. pyramidal tract signs; rt. sided weakness. |
| 4. R.W. | 34 | M | W | Multiple Sclerosis 15 Years | 80 rbc's | 40 | | | Neg. | | Pos. | Far advanced MS |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4. R.W. | 34 | M | W | Multiple Sclerosis 15 Years | 80 rbc's | 40 | | | Neg. | | Pos. | Far advanced MS. Bitemporal disc pallor. Nystagmus; emotional-lability; bilateral pyramidal tract signs. |
| 5. E.S. | 28 | M | W | Post-Traumatic Epilepsy | 0 | 40 | 76 | 717 | Neg. | 0(10) | Neg. | Control |
| 6. B.A. | 32 | M | N | CNS Torulosis | 98 (91% lymphs) | 212 | 13 | 684 | Neg. | 0(10) | Neg. | Control |
| 7. L.D. | 44 | M | W | Undiagnosed encephalopathy? Alcoholic | 100 rbc's | 55 | 100 | 712 | Neg. | 0(10) | Neg. | Control |
| 8. C.J. | 47 | M | N | Pontine Neoplasm ? Tuberculoma | 0 | 36 | 60 | 720 | Neg. | 0(10) | Neg. | Control |
| 9. W.O. | 59 | M | W | Cervical Arthritis Serological Syphilis | 0 | 31 | 87 | 724 | Neg. | 0(10) | Neg. | Control |
| 10. M.P. | 36 | M | W | Post-Traumatic Epilepsy | 0 | 37 | 89 | 728 | Neg. | | Neg. | Control |
| 11. J.O. | 61 | M | W | Amyotrophic Lateral Sclerosis | 0 | 29 | | 714 | Neg. | | Neg. | Control |

TABLE 2.—CLINICAL AND LABORATORY DATA ON MULTIPLE SCLEROSIS AND CONTROL PATIENTS IN WHOM CEREBROSPINAL FLUID CULTURES WERE DONE USING MEDIUM PREPARED IN THIS LABORATORY

| | | | | | *Cerebrospinal Fluid* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Pt.* | *Age* | *Sex* | *Race* | *Diagnosis* | *Cells c. mm.* | *Protein mg. per 100 ml.* | *Sugar mg. per 100 ml.* | *Chlorides mg. per 100 ml.* | *Kolmer* | *Colloidal Gold* | *Culture* | *Remarks* |
| 12. F.K. | 40 | M | W | Multiple Sclerosis 12 Years | 238 rbc's | 20 | | | Neg. | 0112100000 | Pos. | Far advanced bedridden case. Eye signs; diffuse pyramidal tract signs; emotional lability; incontinence. |
| 13. J.T. | 36 | M | W | Multiple Sclerosis 12 Years | 0 | | | | Neg. | | Pos. | Bitemporal disc pallor; bil. pyramidal tract signs; rt. sided weakness. |
| 14. V.P. | 46 | M | W | Multiple Sclerosis 2 Years | 0 | 28 | 75 | 716 | Neg. | 0(10) | Pos. | Marked cerebellar ataxia; nystgamus; pyramidal tract signs; emotional lability |
| 15. J.L. | 35 | M | W | Multiple Sclerosis 5 Years | 0 | 40 | | 702 | Neg. | | Suspicious; probable early forms | Optic atrophy, OD; rt. Babinski; absent abdominals. |
| 16. G.P. | 29 | M | W | Multiple Sclerosis 5 Years | 43 rbc's 3 wbc's | 50 | | | Neg. | | Suspicious; probable early forms | Bitemporal disc pallor; bil. pyramidal tract signs. Scanning speech. |
| 17. W.H. | 41 | M | N | Multiple Sclerosis 13 Years | 4 wbc's | 50 | | | Neg. | 0011221000 | Neg. | Slurred speech; |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | probable early forms | | | | | | | | bil. pyramidal tract signs. Scanning speech. |
| 17. W.H. | 41 | M | N | Multiple Sclerosis 13 Years | 4 wbc's | 50 | | | Neg. | 0011221000 | Neg. | Slurred speech; ataxia; hyperactive DTR'S on right. ? Bitemporal disc pallor. |
| 18. J.W. | 32 | M | W | Probable Multiple Sclerosis—3 Years | 14 wbc's 3 rbc's | 75 | | 744 | Neg. | 0(10) | Neg. | Progressive spastic quadriplegia, nystagmus; positive Lhermitte's signs; Myelogram neg. |
| 19. H.Q. | 34 | M | W | Possible Multiple Sclerosis—5 Years | 0 | 20 | 64 | 716 | | | Neg. | Episodes of ataxia, blurred vision, Neurological neg. except for rt. lateral nystagmus. |
| 20. J.S. | 40 | M | W | Possible Multiple Sclerosis—4 Years | 0 | 27 | 67 | 720 | Neg. | 0(10) | Neg. | Ataxia and blurred vision. Nystagmus only positive finding. |
| 21. T.B. | 25 | M | N | Mediastinal Tuberculosis | 45 rbc's 6 wbc's | 18 | 64 | 707 | Neg. | 0(10) | Neg. | Control |
| 22. J.C. | 30 | M | W | Meniere's Disease | 0 | 15 | | | Neg. | 0(10) | Neg. | Control |
| 23. A.G. | 61 | M | W | Subarachnoid Hemorrhage (Convalescent) | Xantho-chromic 600 rbc's | 48 | 80 | 711 | Neg. | 0001210000 | Neg. | Control |
| 24. M.G. | 63 | M | W | Serological Syphilis | 0 | 74 | | | | 0(10) | Neg. | Control |
| 25. M.H. | 52 | M | W | Chronic Labyrinthitis | 0 | 55 | 55 | 691 | Neg. | 0(10) | Neg. | Control |
| 26. H.H. | 46 | M | W | Wernicke's Syndrome | 0 | 26 | 64 | 684 | Neg. | 0(10) | Neg. | Control |

TABLE 2.—CLINICAL AND LABORATORY DATA ON MULTIPLE SCLEROSIS AND CONTROL PATIENTS IN WHOM CEREBROSPINAL FLUID CULTURES WERE DONE USING MEDIUM PREPARED IN THIS LABORATORY—(*Continued*)

| | | | | | *Cerebrospinal Fluid* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Pt.* | *Age* | *Sex* | *Race* | *Diagnosis* | *Cells c. mm.* | *Protein mg. per 100 ml.* | *Sugar mg. per 100 ml.* | *Chlorides mg. per 100 ml.* | *Kolmer* | *Colloidal Gold* | *Culture* | *Remarks* |
| 27. H.K. | 57 | M | W | Huntington's Chorea | 5 rbc's | 37 | 71 | 743 | Neg. | | Neg. | Control |
| 28. T.M. | 58 | M | W | Syncope, Unknown Etiology | 0 | 37 | 80 | 723 | Neg. | 0(10) | Neg. | Control |
| 29. J.N. | 39 | M | W | Anxiety Reaction | 0 | 51 | 66 | 714 | Neg. | 0(10) | Neg. | Control |
| 30. S.P. | 23 | M | W | Epilepsy, Etiology Undetermined | 0 | 70 | 77 | 741 | Neg. | 0(10) | Neg. | Control |
| 31. J.R. | 41 | M | W | Alcoholic Peripheral Neuritis Serological Syphilis | 0 | 67 | 72 | 710 | Neg. | 0(10) | Neg. | Control |
| 32. A.S. | 37 | M | W | Bronchogenic Carcinoma with cerebral metastases | 0 | 32 | 67 | 682 | Neg. | 0(10) | Neg. | Control |
| 33. R.T. | 36 | M | N | Pernicious Anemia Posterolateral sclerosis | 0 | 45 | 55 | 750 | Neg. | 0(10) | Neg. | Control |
| 34. G.V. | 53 | M | W | Purulent Meningitis (Convalescent) | 1300 wbc's p 83% | 210 | 30 | 684 | Neg. | 0000112222 | Neg. | Control |

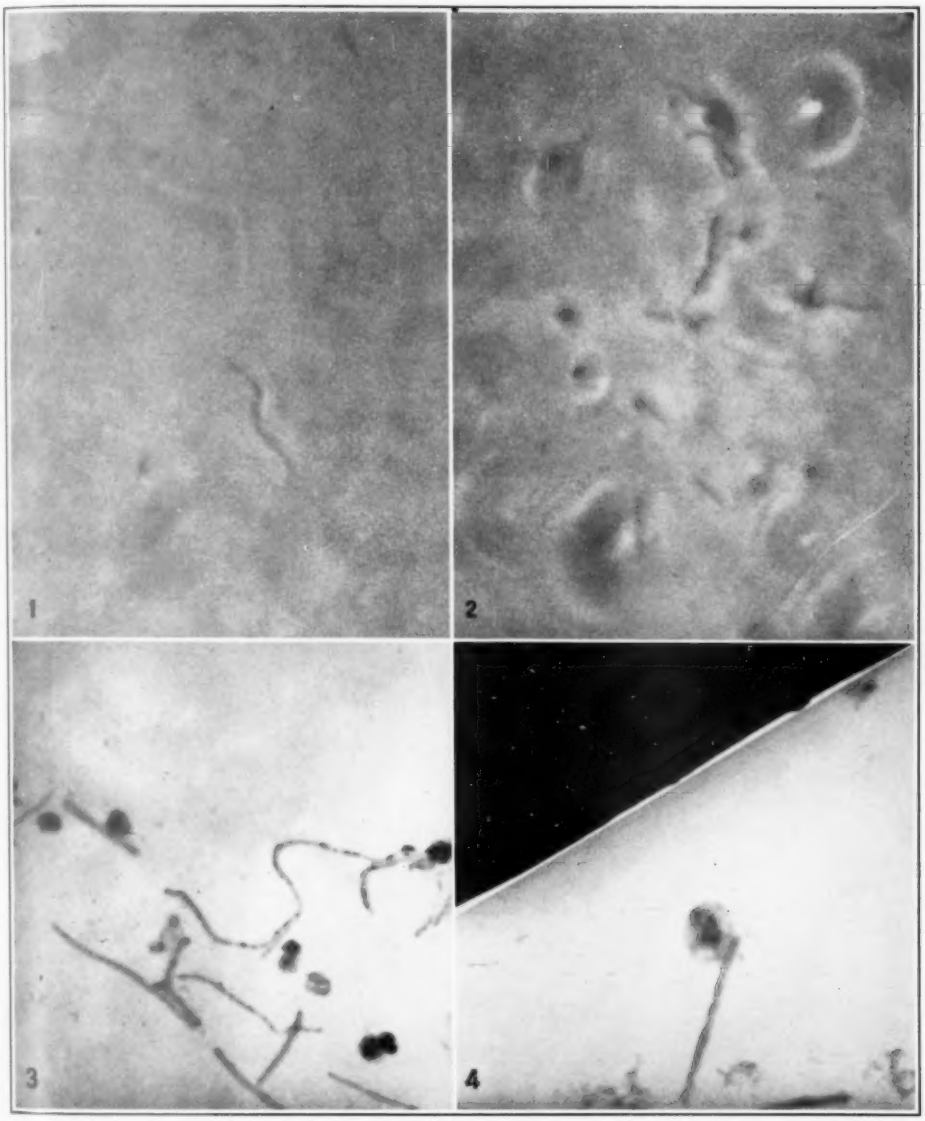


Fig. 1.—Patient F.K. 60-day-old third sub-culture (original culture 5 months old); phase photomicrograph of wet mount; drop of culture fluid was placed on cover slip previously coated with agar to arrest motility: Note large spiral organism and gemma with small tail in lower right hand corner. (4480 ×)

Fig. 2.—Patient F.K. 60-day-old third sub-culture (original culture 5 months old); phase photomicrograph of wet mount; drop of culture fluid was placed on cover slip previously coated with agar to arrest motility: group of organisms depicting typical pleomorphism. (4480 ×)

Fig. 3.—Patient F.K. Electron micrograph of formaldehyde fixed, unshadowed preparation; note large serpentine filaments, occasional slender rod with subterminal gemma and free gemmae. (5000 ×)

Fig. 4.—Patient F.K. Electron micrograph of formaldehyde fixed, unshadowed preparation; terminal gemma attached to filamentous cell; the gemma contains several electron-scattering bodies and is encircled by a membrane. The cell appears to have a spiral ridge.

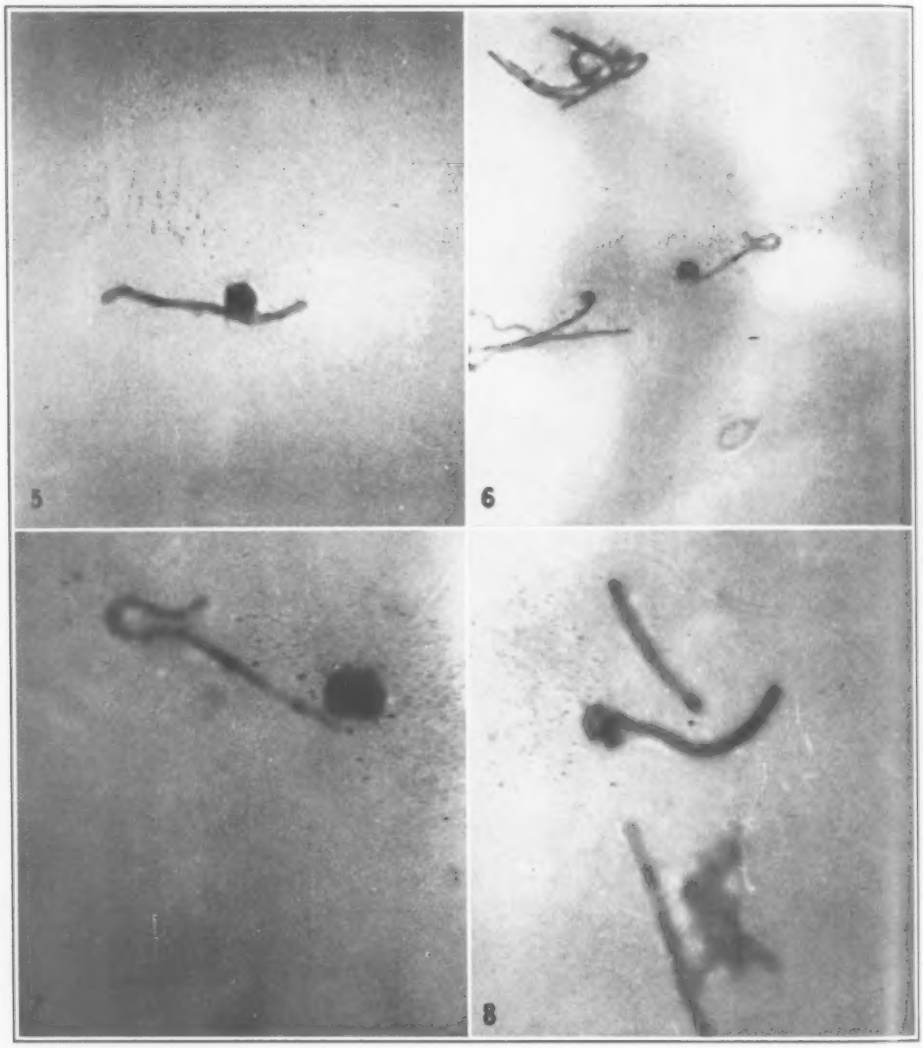


Fig. 5.—Patient J.T. Electron micrograph of formaldehyde fixed, unshadowed preparation; 90-day-old fifth sub-culture (original culture 11 months old); slender, flexuous cell with subterminal gemma. Note numerous electron-scattering protoplasmic bodies (14,500 ×)

Fig. 6.—Patient J.T. Electron micrograph of formaldehyde fixed, unshadowed preparation; 90-day-old fifth sub-culture (original culture 11 months old); group of organisms depicting various shape and sizes (5000 ×).

Fig. 7.—Patient J.T. Electron micrograph of formaldehyde fixed, unshadowed preparation; 90-day-old fifth sub-culture (original culture 11 months old); 14,500 × magnification of organism in Fig. 6.

Fig. 8.—Patient J.T. Electron micrograph of formaldehyde fixed, unshadowed preparation; 90-day-old fifth sub-culture (original culture 11 months old); center organism shows a terminal body possibly representing early gemma formation. (14,500 ×)

**Discussion.** In this highly controversial field a conservative attitude is essential. Several conclusions, however, seem warranted from the present study: (1) The growth obtained is that of a living organism and does not represent an artefact. There is a superficial resemblance to some of the "myelin bodies" describe by Ayres[4] but the organism is readily distinguished from these forms by its morphology, size and motility.

(2) The organism appears to be a spirochete and has many of the morphologic and growth characteristics of other spirochetes as described by DeLamater and his co-workers[15-19]. The organism seems morphologically identical with that described by Steiner, Simons and Ichelson[23,41,45].

(3) The medium employed may be deficient in essential growth requirement as it appears barely to sustain the organism. Therefore, minor deviations from the described technique may result in failure. It is possible that Needham, Voss and Daly did not obtain positive cultures because they autoclaved their medium instead of passing it through a Selas filter for sterilization. The period of centrifugation employed by these investigators was somewhat shorter than ours. In addition, no mention is made of blind sub-culturing, which appears essential[31].

(4) The role of spinal fluid as a

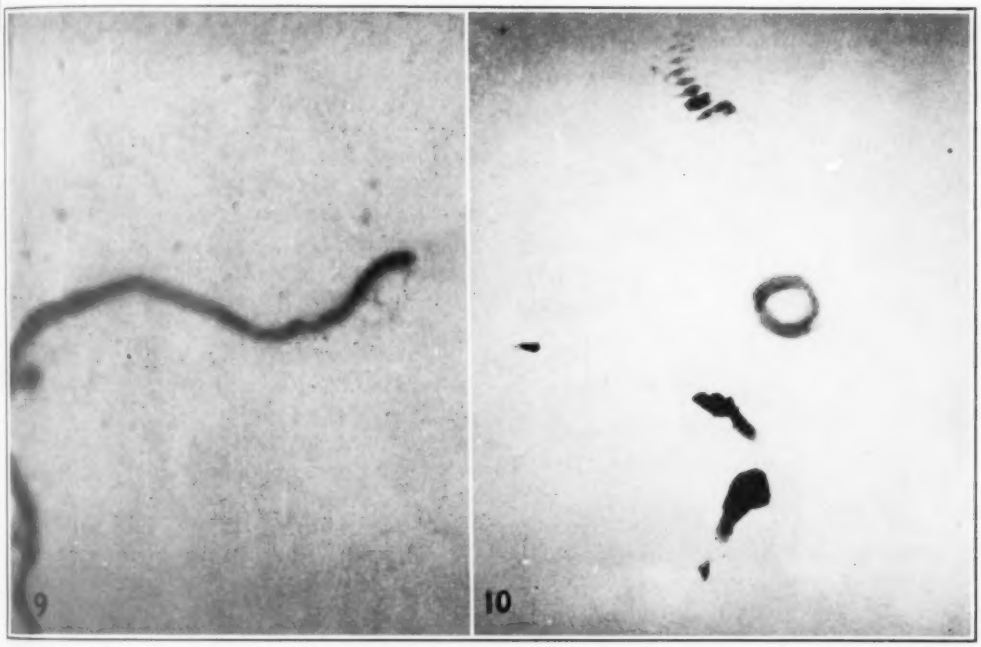


Fig. 9.—Patient J.T. Electron micrograph of formaldehyde fixed, unshadowed preparation; 90-day-old fifth sub-culture (original culture 11 months old); A long, half-completed spiral. (14,500 ×)

Fig. 10.—Patient J.T. Electron micrograph of formaldehyde fixed, unshadowed preparation; 90-day-old fifth sub-culture (original culture 11 months old); A tightly curled flexuous form (14,500 ×)

growth factor is questionable. In several instances suspicious early forms were noted following inoculation of the medium but no further growth was observed. Once the organism has attained full maturity, however, indefinite survival appears to be the rule. Two of the cultures in this laboratory have been growing for more than a year.

Fig. 11.—Patient J.T. Fontana stain; 60-day-old fifth sub-culture from 11 month old original isolation (1100 ×). Short filamentous forms with terminal and subterminal gemmae, one organism without gemma. Note free gemma below.

The present study does not warrant any predications as to the role of this organism in the etiology of multiple sclerosis. Although claims for the infectious nature of this disease have been made on the basis of animal inoculations with body fluids and tissues of patients with multiple sclerosis, the pathologic changes thus produced in the nervous system are generally felt to be nonspecific and their nature highly controversial (Barré[5], Claude[11], Cornwall[13], Cournand[14], Giraud[20], Hudson and Grinker[22], Kauffman[27], Rothwell, Freund and Hornowski[35]). Roach, Rosenberg and Ichelson have prepared an antigen from the organism obtained from positive spinal fluid cultures and have claimed a high degree of positivity for a complement fixation test on the sera from patients with multiple sclerosis[21,33].

Further investigation is definitely indicated. At the present time this laboratory intends to investigate the use of other culture media, including chick embryos and tissue cultures. The organism is to be tested for antibiotic sensitivity. Time lapse photography is planned in an attempt to define further the life cycle of this organism.

**Summary.** Using the cultural technique described by Ichelson, attempts were made to cultivate an organism from the cerebrospinal fluid of patients with multiple sclerosis.

In a preliminary study using medium prepared by Ichelson, positive cultures were obtained in 2 of 4 patients with well established multiple sclerosis. Cultures of the cerebrospinal fluid of 7 control patients were negative.

Medium prepared in our own laboratory yielded positive cultures in 3 patients with multiple sclerosis. In 2 additional multiple sclerosis patients there was a definite suggestion of early forms, but the organism failed to attain maturity. Negative cultures were obtained in 4 additional patients with multiple sclerosis, 21 control patients and in uninoculated medium.

The mature organism resembles a spirochete and is morphologically similar to that reported by Steiner and Simons as occurring in the tissues of multiple sclerosis patients. It appears similar to the organism cultured by Ichelson.

At the present time the cultivation of the organisms cannot be considered as a diagnostic tool nor can any conclusions concerning its role in the etiology of multiple sclerosis be made. There is a definite need for further intensive investigation.

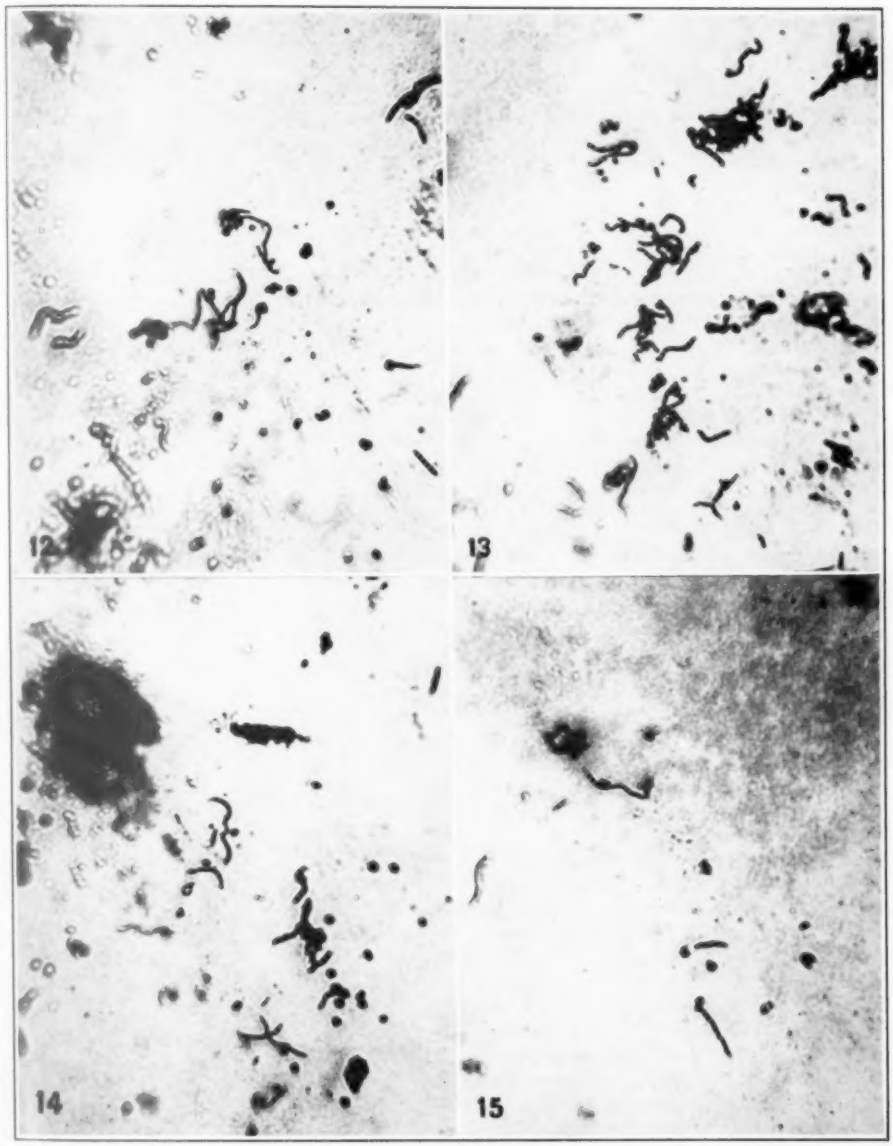


Fig. 12.—Patient J.T. Fontana stain; 60-day-old fifth sub-culture from 11-month-old original isolation (1100 ×). Note free gemmae and gemmae with filamentous bodies of varying lengths.

Fig. 13.—Patient J.T. Fontana stain; 60-day-old fifth sub-culture from 11-month-old original isolation (1100 ×). A large group of organisms demonstrating considerable pleomorphism.

Fig. 14.—Patient J.T. Fontana stain; 60-day-old fifth sub-culture from 11-month-old original isolation (1100 ×). In the center is a large form with convolutions and a centrally located gemma. Note small filament with circular appearance.

Fig. 15.—Patient J.T. Fontana stain; 60-day-old fifth sub-culture from 11-month-old original isolation (1100 ×). Note organism in lower right. End has looped back; possible gemma precursor.

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## SUMMARIO IN INTERLINGUA

### Observationes Preliminari Relative Al Cultivation E Al Morphologia De Un Microorganismo Ab Le Liquido Cerebrospinal De Patientes Con Sclerosis Multiple

Per medio del technica cultural describite per Ichelson, le essayo esseva interprendite de cultivar un organismo ab le liquido cerebrospinal de patientes con sclerosis multiple.

In un studio preliminari, in que le medio preparate per Ichelson esseva usate, culturas positive esseva obtenite in le caso de 2 inter 4 patientes con ben demonstrate sclerosis multiple. Culturas de liquido cerebrospinal ab 7 patientes de controlo esseva negative.

Un medio preparate in nostre proprie laboratorio resultava in culturas positive in tres patientes con sclerosis multiple. In 2 casos additional, un definite suggestion de formas precoce esseva notate, sed le organismo non attingeva su maturitate. Culturas negative esseva obtenite in 4 patientes additional con sclerosis multiple, in 21 patientes de controlo, e in le caso de medio non-inoculate.

Le organismo in stato matur resimila un spirocheta. Illo es morphologicamente simile al organismo que occurre, secundo Steiner e Simons, in le histos de patientes con sclerosis multiple. Apparentemente illo es le organismo jam culturate per Ichelson.

A iste tempore, il non es justificate considerar le cultivation de tal organismos como un technica de valor diagnostic. Similemente, il non es possibile deducer conclusiones con respecto a lor rolo in le etiologia de sclerosis multiple. Il existe definitemente le urgente desiderato de intense investigationes additional.

# A STUDY OF THE EFFECTIVENESS OF CERTAIN ANOREXIGENIC AGENTS*

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There has been considerable discussion concerning the therapeutic effectiveness of anorexigenic agents. Some clinicians are of the opinion that these agents have definite value (Barnes[1], Gelvin and McGavack[4]) while others believe that they are ineffective and that psychogenic factors influencing weight reduction are of primary importance (Melchionna *et al.*[7], Parson and Crispell[9]). It must be admitted that there are many uncontrollable variables to be considered before weight reduction can be ascribed entirely to the therapeutic effectiveness of any particular anorexigenic drug, that is, motivation, emotional needs, social status, the influence of family, friends, and physicians. The first of the following investigations was conducted to determine the anorexigenic effect of phenmetrazine hydrochloride† on patients referred to a weight-reduction clinic. In order to obviate insofar as possible the subjective variables mentioned above, a separate study was conducted on the comparative effects of phenmetrazine hydrochloride and a d-amphetamine sulfate-amobarbital combination‡ on weight reduction in obese mentally-deficient subjects.

**Method.** The first investigation included all adult patients referred to the Weight-Reduction Clinic at the District of Columbia General Hospital during the period of the study. The phenmetrazine and placebo tablets were labeled "A" and "B" respectively, and neither the investigators nor the dietition were informed of the identity of the tablets administered. The study was continued for 16 weeks with half of the patients receiving phenmetrazine and half receiving the placebo for alternating 8-week periods. Each patient was given one hour's instruction by the dietitian which included the prescription of an individualized diet for weight reduction based on the food history and information regarding the family background. The patient was then given Compound "A" (25 mg. per tablet) or "B" and instructed to take 1 tablet, three times a day, 1 hour before each meal. On the weekly return visit, the patient's weight was recorded and observations were made regarding the subjective effect on appetite

*This investigation was supported in part by a research grant (PHS B–178) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

†The phenmetrazine hydrochloride (Preludin) used in these studies was supplied by Geigy Pharmaceuticals, Ardsley, New York.

‡Trade name, Dexamyl.

and the occurrence of undesirable side reactions. Of the 106 patients included in the study, 55 completed a course of both phenmetrazine and placebo, 40 received phenmetrazine only, and 11, placebo only. The mean weekly weight changes were computed and statistically evaluated.

In the second investigation, the anorexigenic effects of phenmetrazine hydrochloride, d-amphetamine sulfate-amobarbital combination, and a placebo were studied on obese mentally-deficient subjects at the District Training School. Their ages ranged from 10 to 65 years, and their average I.Q. was 37.

The patients were divided into three groups distributed as equitably as possible according to age, sex, intelligence quotient, height, and initial weight. Fifteen patients received phenmetrazine (25 mg. b.i.d.), 14 patients received d-amphetamine sulfate (5 mg. b.i.d.), and 14 patients were given the placebo at similar intervals. No diets were prescribed, and all subjects were served the same meals containing an average of approximately 2,700 calories per day. Considering energy output, such a diet, if entirely consumed, would provide calories far in excess of need.

The phenmetrazine, d-amphetamine, and placebo were labeled "A", "B", and "C", respectively, and neither the physician nor the individual administering the medication was aware of the identity of the drug administered. Each patient received 2 tablets a day, one hour before the noon and evening meals. After 12 weeks, the dosage was doubled for those patients showing little or no weight change, and the number of placebo tablets was correspondingly increased.

The study was terminated after 28 weeks. Observations were made daily for side effects such as hypertension, hyperactivity, and insomnia. Individual weights for each group were recorded at 4-week intervals. The average weight loss for each of the three groups was determined for the period on medication, and the means were evaluated statistically.

**Results.** The results of the study conducted at the Weight-Reduction Clinic are presented in Table 1. For the 55 patients who completed the program of alternate periods on phenmetrazine and the placebo, the average weight loss was 1.25 lb. per week with phenmetrazine and 0.19 lb. per week with the placebo. The weight loss during phenmetrazine therapy was significantly greater than the weight loss during the period on the placebo ($p<.01$). If the placebo period is considered to represent the average weight loss due to diet and environment, then the effect of phenmetrazine increases the weight loss slightly more than 1 lb. a week. While the usual course on each drug was planned for 8 weeks, variations in the length of observation periods occurred either because the patient dropped out of the study before the period was completed or because he did not return for a check-up on the eighth week. The average period on phenmetrazine was 9.07 weeks and on the placebo, 7.96 weeks.

These patients were randomly distributed between the phenmetrazine and placebo at the start of the study, but in the final group there were 34 who began therapy on phenmetrazine and 21 on the placebo. Table 2 presents the mean weekly weight loss with the patients separated into groups by the drug on which the patient began therapy. It will be noted that when patients were started on phenmetrazine, there was an average weight loss of 1.60 lbs. per week compared with 0.43 lb. for those who began on the placebo, representing a difference of 1.15 lbs. due to the drug. After the crossover, a patient who had been on the placebo lost an additional 1.00 lb. per week on phenmetrazine, while those who began weight reduction on phenmetrazine showed a negligible further loss when switched to the placebo. To correct for the bias introduced by the larger group starting on phenmetrabine, an adjusted average was computed, which indicated that had the groups been equal, the weight loss would have been 1.30 lbs. per week on phenmetrazine and 0.26 lb. per week on the placebo.

There were 51 patients who did not complete the study for various reasons.

Of these, 40 received phenmetrazine only, with an average weight loss of 1.13 lbs. per week for 7.83 weeks. The 11 patients who received only the placebo had an average weight loss of 0.71 lb. per week for 3.73 weeks.

Table 3 presents the incidence of side effects recorded in the mentally-alert group. It should be noted that the frequency of side effects was almost as great in the placebo group as in those receiving phenmetrazine.

The results of the investigation on the effect of anorexigenic agents on mentally-deficient subjects are presented in Table 4. There was wide individual variation in weight loss. At the end of the 28-week period, the subjects on phenmetrazine had an average weight loss of 16.0 lbs., ranging from 2.0 to 35.5 lbs. The group on d-amphetamine sulfate had an average weight loss of 14.7 lbs. ranging from a gain of 7.0 lbs. to a loss of 42.0 lbs., with 2 subjects gaining weight. The subjects on the placebo lost an average of 5.7 lbs., ranging from a gain of 17.0 lbs. to a loss of 23.0 lbs., with 3 subjects showing a gain and one, no change. The mean weight losses on phenmetrazine and d-amphetamine sulfate were statistically significant at the 1% level while that on the placebo was not significant. The difference in weight loss between the phenmetrazine and placebo groups was statistically significant at the 2% level, but because of the wide range of the d-amphetamine group and the fact that there was some loss in the placebo

TABLE 1.—WEIGHT LOSS IN MENTALLY-ALERT PATIENTS WHO RECEIVED BOTH PHENMETRAZINE AND PLACEBO

| | *No. of Subj.* | *Avg. Period on Drug (Wks.)* | *Avg. Weight Loss (Lbs.)* | *Avg. Weight Loss/Week* |
|---|---|---|---|---|
| Phenmetrazine | 55 | 9.07 | 11.37 | 1.25* |
| Placebo | 55 | 7.96 | 1.55 | 0.19 |

* Significant difference from placebo, $p < .01$

TABLE 2.—MEAN WEEKLY WEIGHT LOSS IN MENTALLY-ALERT PATIENTS BY DRUG ON WHICH PATIENT BEGAN THERAPY

| *Starting Drug* | *No. of Subjects* | *Pounds Lost Per Week* | |
|---|---|---|---|
| | | *Phenmetrazine* | *Placebo* |
| Phenmetrazine | 34 | 1.60 | 0.09 |
| Placebo | 21 | 1.00 | 0.43 |

TABLE 3.—SIDE EFFECTS REPORTED BY 55 MENTALLY-ALERT PATIENTS WHO RECEIVED BOTH PHENMETRAZINE AND PLACEBO

| | *No. of Patients* | |
|---|---|---|
| | *Phenmetrazine* | *Placebo* |
| Nervousness: | 9 | 8 |
| Insomnia, slight or occasional: | 7 | 3 |
| Constipation: | 7 | 3 |
| Dizziness: | 2 | 2 |
| Headache: | 1 | 1 |
| More energy: | 7 | 2 |

group, the difference between these two groups was not statistically significant. Increasing the dosage of both anorexigenic agents did not alter the weight reduction response; apparently the initial dosage provided the maximum response obtainable.

**Discussion.** The results demonstrate that in both the mentally-alert and mentally-deficient groups, the administration of anorexigenic agents caused significant reduction in weight. The weight changes induced by phenmetrazine seemed to be somewhat more significant than those induced by d-amphetamine. This may be attributed in part to the greater variation in weight changes induced by the latter drug. The loss which occurred with the placebo in the mentally-deficient group might be attributed to seasonal variations as well as other unidentified factors but was not sufficient to lessen the significance of the response to both phenmetrazine and d-amphetamine. An analysis of a sample of the nontreated mentally-deficient population (26 subjects) during the period of this study indicated a weight loss of 1.88 lbs., a value not significantly different from the loss obtained in the placebo group.

Only in the mentally-alert group of subjects was it possible to determine the subjective effects of phenmetrazine. As illustrated in Table 3, in the 55 mentally-alert subjects who completed a course on both phenmetrazine and placebo, 9 complained of "nervousness" on phenmetrazine, particularly during the first few days of drug ingestion; however, it should be pointed out that 8 of those receiving the placebo also complained of "nervousness." Insomnia was reported by 7 subjects on phenmetrazine (usually noted only for a few days or when 2 tablets were taken in the evening); 3 of the subjects on the placebo also complained of insomnia. It may also be of interest that in the mentally-deficient subjects even large doses of the anorexigenic agents did not cause apparent overstimulation or excitation. Mild constipation was reported by 7 subjects on phenmetrazine and 3 subjects on placebo. These side effects were usually noted only when the dosage was increased to 2 tablets, three times a day, and it is interesting to note that doubling the placebo dose caused almost as many side effects as doubling the phenmetrazine dose.

TABLE 4.—EFFECT OF ANOREXIGENIC AGENTS ON MENTALLY-DEFICIENT SUBJECTS

| | *No. of Subjects* | *Mean Age (Yrs.)* | *Mean I.Q.* | *Period on Drug (Wks.)* | *Avg. Wt. Loss (Lbs.)* |
|---|---|---|---|---|---|
| Phenmetrazine | 15 | 32 | 33 | 28 | 16.0* |
| D-amphetamine | 14 | 31 | 43 | 28 | 14.7 |
| Placebo | 14 | 30 | 34 | 28 | 5.7 |

* Significant difference from placebo, $p < .02$

The patients' comments on drug effectiveness were also evaluated for the 55 clinic patients who received both the phenmetrazine and the placebo. A marked reduction in appetite was noted by 41 patients on phenmetrazine with only 1 noting no effect. By contrast, over half the patients on the placebo noted only a slight or irregular reduction in appetite, and 8 reported no effect. The fact that 16 claimed a marked appetite reduction on the pla-

cebo, however, confirms the consistent presence of placebo reactors in any group that is subjectively evaluated. This is similarly borne out by the fact that while 31 patients considered phenmetrazine better than the placebo, 6 found the placebo more effective, and 7 reported no difference. A few patients who reported no difference between the drugs or marked effectiveness of both, lost weight on phenmetrazine and gained weight on the placebo.

Marked individual variation in weight reduction occurred in both the mentally-alert clinic group and in the mentally-deficient institutionalized group. A possible explanation for this phenomenon will be presented.

The information currently available suggests that both phenmetrazine and d-amphetamine influence weight reduction primarily by their central effects. Previous studies have demonstrated that marked changes in satiety may be induced by either chemical or electrical lesions of subcortical areas and particularly the posterior hypothalamus (Brobeck, Tepperman and Long[3], Hetherington and Ransom[5], Owen, Parson and Crispell[8]). The exact mechanism by which such lesions cause alterations in appetite are not known, but it has been postulated that a reciprocal relationship exists between the appetite-stimulating center and the appetite-inhibitory center and that destructive lesions of either of these areas result in alterations of satiety and subsequent changes in weight (Brobeck[2]).

Although the subcortical or visceral areas of the brain have been considered largely responsible for changes in consciousness, temperature regulation, appetite, and the like, it is not unreasonable that such functions are interdependent and that drugs affecting primarily subcortical regions may influence simultaneously several activities of the central nervous system. It has already been recognized that the phenothiazine derivatives and rauwolfia alkaloids, which presumably act primarily on subcortical structures, may cause alterations in weight (as well as changes in behavior) not necessarily attributable to changes in fluid balance. While it may be argued that these drugs act primarily on hypothalamic centers, one cannot logically conceive that specific regions of the brain function independently and autonomously, in view of their neural connections with other brain areas. The fact that barbiturates, at least in small doses, are ineffective for the control of satiety would seem to confirm the concept that the regulation of food intake may be primarily under subcortical influences although the importance of cortical factors cannot be minimized.

As previously indicated, there is as yet no satisfactory understanding of all the mechanisms responsible for the regulation of food intake. Mayer[6] has proposed that the concentrations of glucose reaching the centers controlling appetite may have a regulating influence. The facts presented to support this thesis would appear untenable since the arteriovenous differences taken from regions other than the brain obviously cannot be used to reflect what may be taking place in the brain. In fact, neither in starvation nor in diabetes has there been reported any significant changes in cerebral arteriovenous glucose uptake. Furthermore, the determination of over-all cerebral arteriovenous glucose differences will not necessarily indicate the rate of uptake of this essential substrate by specific brain areas, nor would such studies be significant even if the rate of cerebral blood flow were simultaneously determined for quantitative estimation of over-all cerebral glucose utilization.

The observation that various agents such as phenothiazines, rauwolfia alkaloids, isoniazid and iproniazid, may influence appetite would seem to suggest that the regulation of the above activity may be determined by central neurohumoral factors since these agents presumably act by influencing either the inhibition of enzyme activity concerned with the formation of various neurohumors or conceivably affect their rate of destruction. Even if these drugs (ataractics, "psychic energizers," or anorexigenic agents) inhibited specific metabolic reactors, there would necessarily be a secondary diminution of neurohumoral production. Although there is no evidence as yet that phenmetrazine influences monamine oxidase or choline esterase activity, it is conceivable that it may influence appetite by either a direct or indirect action on neurohumoral activity in the specific appetite centers.

The influence of cortical activity on food intake cannot be completely ignored. It is generally recognized that cultural, educational, and other environmental factors mostly under cortical control may cause marked changes in food intake and weight regardless of the use of adjuncts such as centrally-acting drugs in some obese subjects; this provides the rationale for the advocates of psychotherapy for the treatment of obesity. It should not be surprising, therefore, that there is considerable variability in the response to anorexigenic agents even in the mentally-deficient population, as evidenced in the present study.

Despite the lack of available and necessary information, it may be of some interest to conjecture regarding the various neural mechanisms concerned with the control of weight. Certainly one cannot ignore such factors as the total rate of energy production or glucose utilization. Even if the concentration of glucose in the blood circulating through the various regions of the brain were significant, it would ultimately have to exert its influence through alterations in neural activity.

The experimental work in animals previously referred to seems to be sufficiently conclusive to establish the existence of an appetite-stimulating and an appetite-inhibitory center in the hypothalamus acting reciprocally in relation to each other and under "normal" circumstances maintaining weight at a reasonably constant level. There can be no doubt that before the evolution of the cortex these centers must have been under the control of and influenced by impulses from other subcortical regions and the peripheral nervous system (spinal cord and autonomic nervous system).

As indicated previously, centripetal impulses from various cortical regions must play upon the appetite centers in man, and in turn, centrifugal impulses from these centers are directed to various cortical regions. This concept is diagrammatically illustrated in Fig. 1. Although its simplicity and lack of unequivocal evidence is recognized, it may be helpful in suggesting the many complicated factors that are concerned with weight control, both normal and pathologic.

**Summary and Conclusions.** Double blind studies of the effectiveness of two anorexigenic agents were conducted. Phenmetrazine hydrochloride and a placebo were compared in a group of obese, mentally-normal subjects, and, in order to obviate insofar as possible the influence of suggestion, phenmetrazine hydrochloride, d-amphetamine sulfate, and a placebo were compared in a group of mentally-deficient subjects.

In both the mentally-alert and mentally-deficient subjects, there was a significant reduction of weight with

phenmetrazine but no significant change during placebo administration. Subjective side reactions evaluated only among the mentally-normal patients disclosed no apparent difference between phenmetrazine and the placebo. In the mentally-deficient group, the weight loss induced by d-amphetamine sulfate was similar to that obtained with phenmetrazine.

It is postulated that these drugs act primarily in subcortical areas, probably by influencing localized neurohumoral activity. In view of the almost certain influence of the cortex and spinal cord, as well as the subcortex, upon appetite, it should not be surprising that there is considerable variability in individual response to anorexigenic agents.

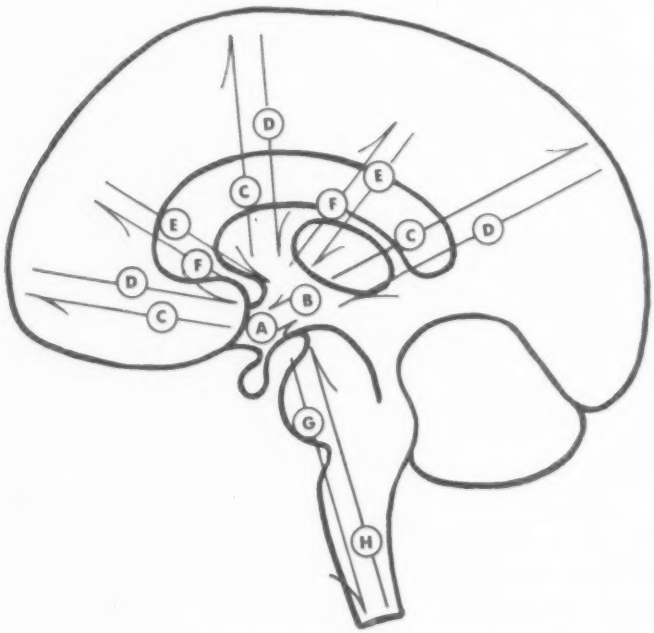


Fig. 1.—Neural factors in weight control. (*A*) Appetite-stimulating center. (*B*) Appetite-inhibiting center. (*C*) Centrifugal cortical impulses from *A* and *B*. (*D*) Centripetal impulses to *A* and *B* from cortex. (*E*) Subcortical impulses to *A* and *B*. (*F*) Impulses from *A* and *B* to subcortical regions. (*G*) and (*H*) Impulses to and from peripheral nervous system.

ACKNOWLEDGMENT: The authors wish to express their appreciation to Mrs. Marie Negron, Mrs. Marjorie Krewson, and Miss Gertrude Haugan for their assistance with this study.

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## SUMMARIO IN INTERLINGUA

### Un Studio Del Efficacia De Certe Agentes Anorexigene

Esseva executate studios bis-occulte in re le efficacia de duo agentes anorexigene. Hydrochloruro de phenmetrazina e un medication fictitie esseva comparate in un gruppo de obese, mentalmente normal subjectos, e—pro obviar, in tanto que possibile, le effecto de suggestion involuntari—hydrochloruro de phenmetrazina, sulfato de d-amphetamina, e un medication fictitie esseva comparate in un gruppo de subjectos con deficientia mental.

In ambe gruppos—illo del subjectos mentalmente normal e illo del subjectos mentalmente deficiente—un grado significative de reduction de peso esseva notate con le uso de phenmetrazina, sed nulle significative alteration occurreva durante le administration del medication fictitie. Le subjective reactiones lateral—evalutate solmente in le mentalmente normal patientes—revelava nulle apparente differentia inter phenmetrazina e le medication fictitie. In le gruppo del mentalmente deficiente subjectos, le perdita de peso effectuate per sulfato de d-amphetamina esseva simile a illo effectuate per phenmetrazina.

Es postulate que iste drogas age primarimente in areas subcortical, probabilemente per influentiar localisate activitate neuro-humoral. Viste le quasi indubitabile influentia que le cortice e le medulla dorsal—si ben como le subcortice—exerce super le appetito, il non pote esser reguardate como surprendente que un alte grado de variabilitate existe in le responsas individual a agentes anorexigene.

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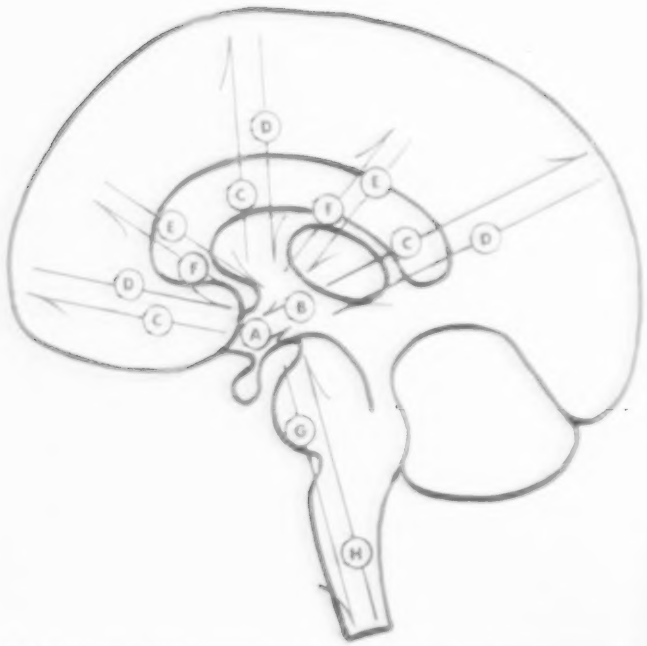


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# RENAL BIOPSY CHANGES WITH PHEOCHROMOCYTOMA*

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Kidney biopsy findings from patients with essential hypertension and chronic pyelonephritis with hypertension, utilizing material collected from 1350 patients by Dr. Reginald H. Smithwick and associates during sympathectomy operations, have recently been reviewed (Merriam, Sommers and Smithwick[6], Saltz, Sommers and Smithwick[8], Sommers, Relman and Smithwick[9]). Hypertension accompanying pheochromocytomas differs from the more common types, partly because the responsible chemical substances are known, their source can be removed, and the increase in blood pressure is usually reversible. Kidney biopsies in persons with pheochromocytoma have histologic changes distinguishable from those in other types of hypertension, although not diagnostic of pheochromocytoma. These histopathologic findings may cast light upon the relationship of some adrenal medullary hormonal effects on the kidney to this type of hypertension.

Renal tissue was obtained for review from 9 of the patients who underwent removal of a pheochromocytoma at the Massachusetts Memorial Hospitals in the 12 years, 1947–1958.

**Materials and Methods.** There were 11 surgical kidney biopsies, about 12 × 6 × 4 mm. in size, taken from 9 patients. The diagnosis of pheochromocytoma was substantiated pathologically in each case. In one case the patient underwent bilateral lumbodorsal sympathectomy and kidney biopsy, and 8 years later he had a pheochromocytoma removed and a second kidney biopsy. In another patient when the pheochromocytoma was removed a kidney biopsy was obtained; 6 years later a second kidney biopsy was performed at the time of cholecystectomy. Two patients had a unilateral lumbodorsal sympathectomy in addition to excision of the pheochromocytoma and kidney biopsy. In the remaining 5 patients a kidney biopsy was performed at the time of pheochromocytoma removal without additional surgery. There were no deaths from the surgical procedures and all patients were much improved postoperatively.

Zenker-fixed or frozen-dried, paraffin-embedded specimens were stained with hematoxylin and eosin and in some cases also with Verhoeff elastic tissue or periodic acid Schiff (PAS) methods. Pathologic alterations in the renal glomeruli, juxta-glomerular apparatus, tubules, stroma, and blood vessels were recorded for each specimen. Assays of 5 pheochromocytomas for catechols, epinephrine and norepinephrine were available (Table 1).

**Clinical Findings.** The patients ranged in age from 12 to 44 years. Two patients were in the second decade; 3 each were in the third and fourth decades; 1 patient was in the fifth decade. They manifested the symptoms of a pheochromocytoma from 5 months to 6 years prior to removal of the tumor. In all patients the blood pressure reached levels considerably above normal, particularly at the time of paroxysmal pressure elevations. Systolic pressures as high as 300 mm. Hg and dia-

*Aided in part by a grant from the Massachusetts Heart Association.

stolic pressures as high as 190 mm. Hg were recorded. Postoperatively the blood pressure levels remained within a much lower range (Table 1).

There were 4 patients who had blood urea or nonprotein nitrogen levels that were normal both before and after operation. One patient had a normal blood urea level preoperatively, but a similar test was not done postoperatively. In 2 patients the determination was slightly elevated preoperatively and within normal limits postoperatively. Slightly abnormal elevations were noted in 2 patients postoperatively. Phenolsulphonphthalein excretion tests were recorded on 8 patients, and all except one fell within a normal range at 2 hours. In this patient the 2-hour excretion was 53% (Table 2).

Intravenous pyelography was performed on each patient. The roentgenographic films were interpreted as normal in 5 cases, evidence of pyelitis was found in 3 patients, and one patient had a bilateral double renal pelvis. Urinalyses were recorded in each case. Hematuria and persistent glycosuria were not found. Three patients showed 1+ albuminuria while 2+ albuminuria was found in 1 patient. Casts were noted in 3 cases.

**Pathologic Observations.** Renal arteries and large arterioles showed comparatively more severe alterations than the smaller arterioles, with hyper-

TABLE 1.—PATIENTS' AGES, DURATION OF SYMPTOMS, AND REPRESENTATIVE BLOOD PRESSURE LEVELS BEFORE AND AFTER REMOVAL OF PHEOCHROMOCYTOMA

| *Patient* | *Sex* | *Age, Year* | *Duration of Symptoms, Years* | *Preoperative During Paroxysmal Elevation* | *Postoperative* |
|---|---|---|---|---|---|
| D.A.* | F | 12 | 11/12 | 300/180 | 120/70 |
| J.W. | M | 13 | 5/12 | 180/160 | 120/80 |
| F.B. | M | 22 | 3 | 280/190 | 130/70 |
| B.T. | F | 26 | 10/12 | 300/140 | 130/80 |
| R.H.† | M | 28 | 6/12 | 230/130 | 150/90 |
| M.W.‡ | F | 33 | 6 | 200/120 | 120/80 |
| D.N.§ | F | 35 | 7/12 | 214/138 | 124/90 |
| M.M. | M | 39 | 16/12 | 300/170 | 110/90 |
| F.M.‖ | F | 44 | 3 | 200/130 | 120/80 |

*Assay of tumor: 0 mg./gm. epinephrine, 1.2 mg./gm. norepinephrine.
†Assay of tumor: 1.7 mg./gm. epinephrine, 2.4 mg./gm. norepinephrine.
‡Assay of tumor: catechol 0.3 mg./gm.
§Assay of tumor: 2.1 mg./gm. epinephrine, 1.0 mg./gm. norepinephrine.
‖Assay of tumor: 10.4 mg./gm. epinephrine, 7.0 mg./gm. norepinephrine.

TABLE 2.—PHENOLSULPHONPHTHALEIN EXCRETION AND BLOOD UREA OR NONPROTEIN NITROGEN DETERMINATIONS

| | *Preoperative P.S.P. Excretion* | | *Blood Urea or Nonprotein Nitrogen* | |
|---|---|---|---|---|
| *Patient* | *15 min. %* | *2 hrs. %* | *Preoperative mg./100 ml.* | *Postoperative mg./100 ml.* |
| D.A. | 32 | 96 | BUN 20 | BUN 29 |
| J.W. | 32 | 95 | BUN 26 | BUN 7 |
| F.B. | 25 | 67 | NPN 36 | NPN 29 |
| B.T. | 7 | 85 | NPN 40 | NPN 30 |
| R.H. | 20 | 70 | NPN 34 | BUN 13 |
| M.W. | 32 | 61 | NPN 27 | NPN 27 |
| D.N. | — | 53 | NPN 43 | NPN 30 |
| M.M. | 20 | 65 | NPN 40 | NPN 45 |
| F.M. | — | — | BUN 12 | — |

trophied arterial smooth muscle, irregular thickening and splitting of the internal elastic membranes, and localized foci of subendothelial arterial fibrosis. Small arterioles were usually moderately thickened by muscular hypertrophy, often with hydropic changes, and rarely with foci of fibrinoid necrosis (Fig. 1). Hyalinization or fibrosis of arterioles was not seen. Larger renal veins were quite congested, as if there were some obstruction to venous blood flow, possibly by hilar muscular sphincters.

Glomeruli had generally a slight stiffening of their capillary walls and a simplification of their structure. Most interesting was an unusual local dilatation of capillaries either at the glomerular root or in the peripheral loops. The dilatation of root capillaries resembled a jet effect of blood released rather abruptly from the concentrically hypertrophied, narrowed, afferent arterioles usually present (Fig. 2). The juxta-glomerular apparatus showed no consistent alteration. Tubules were usually slightly dilated, with cloudy swelling, as seen in situations of mild ischemia (Sommers, Relman and Smithwick[9]). Stromal scarring and glomerular atrophy hyalinization were not prominent.

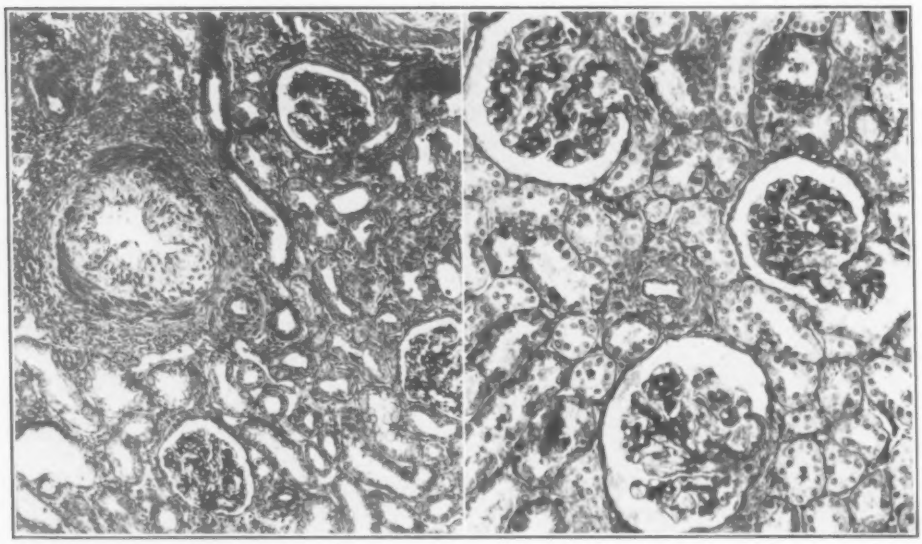

Fig. 1 Fig. 2

Fig. 1.—Considerable hypertrophic thickening of a large artery at the left, with extreme subendothelial edema. Arterioles shown just above and below the thickened artery, and at glomerular roots, are less affected. Case R.H., hematoxylin and eosin, × 125.

Fig. 2.—Dilated afferent capillary pool shown in three glomeruli. The afferent arteriolar connection is evident in the glomerulus at the top. A moderately hypertrophied arteriole is present in the center. Case D.N., PAS trichrome, × 250.

The 2 cases in which 2 kidney biopsies were available, 6 and 8 years apart, provided a contrast. In the man (R.H.) who had a bilateral lumbodorsal sympathectomy and subsequently persistent hypertension for 8 years prior to removal of the pheochromocytoma and

a second kidney biopsy, there was a progression of renal arteriolar thickening, a fibrous replacement of arteriolar smooth muscle, and also glomerular ischemia with atrophy and basement membrane thickenings. The man (F.B.) who had the pheochromocytoma removed and was normotensive for 6 years prior to a second kidney biopsy at the time of cholecystectomy had retained focal abnormalities of the arteriolar and glomerular capillary walls with pooling of PAS-positive material 6 years later, but without any evident permanent significant narrowing either of arterioles or capillaries. There were no clinico-pathologic distinctions found between the kidney changes that accompanied the 2 tumors which secreted mostly epinephrine and the 2 pheochromocytomas that produced more norepinephrine.

**Discussion.** The renal biopsy findings with pheochromocytoma have apparently not previously received much attention. It is of interest that the most striking alterations occurred in the renal arteries and consisted essentially of muscular hypertrophy and secondary degenerative changes. The arterioles were relatively less narrowed by muscular spasm and hypertrophy. This situation is the reverse of that found in essential hypertension, in which small renal arterioles are the most thickened and in which arteries and large arterioles may at first appear dilated and only subsequently become hypertrophied (Sommers, Relman and Smithwick[9]).

Glomerular hyperemia is more characteristic of the hypertension accompanying pheochromocytoma, and conversely glomerular ischemia characterizes an established essential hypertension. The jet-like blood flow into the glomerulus may dilate the so-called afferent pool of capillaries at its root. Lynch[5] has recently commented on the dynamic alterations of which the glomerular capillaries are capable.

To explain the characteristic reversion of blood pressure levels to normal after pheochromocytoma removal, it is significant that smaller renal arterioles are hypertrophied and locally edematous, but they are not fibrotic or sclerotic, as frequently occurs in cases of essential hypertension with a comparable degree of arteriolar thickening. Muscular hypertrophy and edema of arterioles are reversible changes, while fibrous scarring of vessel walls generally is not. Only the man who had hypertension for an 8-year period between his first kidney biopsy and removal of the pheochromocytoma showed fibrosis of arteriolar walls.

The hormones of the adrenal medulla are epinephrine and norepinephrine. Epinephrine has a central nervous stimulatory effect and a vasodilating action on some peripheral blood vessels. Norepinephrine is said not to have any significant central nervous action. It produces constriction of small blood vessels. The strong vasoconstrictor and blood pressure raising properties of norepinephrine, and its presence in adrenergic nerves and chromaffin cells, have directed attention to the possibility of a preponderant liberation of this substance in some chromaffin tumors (Euler[4]). A clear indication that norepinephrine was the causative factor in the hypertension accompanying pheochromocytoma was obtained by Engel and Euler[3] in 1950. They found a greatly increased output of norepinephrine in the urine of 2 such cases, and this has been later confirmed and extended.

Pickford and Watt[7] stated that norepinephrine and epinephrine have no direct action on kidney activity but affect it by altering conditions in the systemic circulation. They concluded that the increased glomerular filtration

rate with norepinephrine is due to a rise in systemic pressure, with only a moderate degree of renal vasoconstriction. DiSalvo *et al.*[2] concluded that epinephrine produced blood pressure and other effects mainly through cardiac stimulation, and norepinephrine by its action on peripheral blood vessels. Corcoran, Wagner and Page[1] found that in hypertensives norepinephrine increased the renal vascular resistance proportionately more than it raised the systemic blood pressure. Studies by Tobian and Fox[10], using norepinephrine infusions in dogs, showed that a loss of intracellular potassium from arterial smooth muscle was associated with the arterial contraction produced.

The renal pathologic findings in the present group of pheochromocytomas would favor a relatively greater secretion of norepinephrine. The laboratory data and the clinical appraisal of kidney activity indicated that the excretion function of the kidney was essentially unaltered in the patients with pheochromocytoma.

**Summary.** Kidney biopsies and laboratory tests of renal function from 9 patients with pheochromocytoma have been evaluated. Hypertension with pheochromocytoma is associated with glomerular hyperemia and with hypertrophy and degenerative changes affecting the renal arteries more than the small arterioles, the reverse of the findings with typical essential hypertension. The observations are discussed in relation to vasoconstrictor effects of the adrenal medullary hormones.

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## SUMMARIO IN INTERLINGUA

### Alterationes In Specimens De Biopsia Renal Ab Patientes Con Pheochromocytoma

Esseva evalutate biopsias renal e tests laboratorial del function renal in 9 patientes con pheochromocytoma. Hypertension con pheochromocytoma es associate con hyperemia glomerular e con hypertrophia e alterationes degeneratori que affice le arterias renal plus que le micre arteriolas, per contrasto con le constatationes in typic hypertension essential. Le constatationes es discutite in relation al effectos vasoconstrictori del hormones adreno-medullar.

# THE CARDIOVASCULAR EFFECTS FOLLOWING INTRACISTERNAL POTASSIUM CHLORIDE INFUSION*

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Elevation of blood pressure and other systemic reactions result from the intracisternal injection of relatively small quantities of potassium salts in experimental animals (Bekaert[2], Calma and Wright[3], Cloette and Fischer[5], Downmann and MacKinzie[8], Koenigstein[10], Luesen[12], Mullen, Hastings and Lees[13], Resnick *et al.*[16], Stern and Chvoles[18]). The production of cardiac arrhythmias by this method has also been recorded (Walker *et al.*[20,21]). However, there have been no careful studies correlating the blood pressure, electrocardiographic changes, and the effects of various antihypertensive drugs on the observed changes.

The purpose of this study was to observe and record in detail some of the electrocardiographic and blood pressure alterations produced by intracisternal KCl injections, to note the effect of various autonomic nervous system blocking agents on these changes, and to correlate the blood and cerebrospinal fluid electrolyte levels with the observed cardiovascular changes. The mechanisms involved are of considerable experimental and probable clinical interest.

**Methods and Materials.** Two milliliters of varying concentrations (100 to 2000 mEq./L.) of potassium chloride solutions were administered within 5 seconds intracisternally to dogs weighing 10 to 13 kilograms. This experiment was performed in 19 dogs. Pentobarbital anesthesia was used in dogs No. 1 to 6; Thiopental anesthesia was used in the remaining experiments because of its known and demonstratively lesser cardiac vagolytic effect (Goodman and Gilman[9]). Simultaneous electrocardiograms and intra-arterial (femoral) blood pressures were recorded with the Sanborn Twin-Viso Recorder and Sanborn Electromanometer respectively. Endotracheal airway was provided each animal, with intermittent positive pressure respirations. All blood specimens for analysis were femoral artery samples. Cerebrospinal fluid was first obtained from a needle introduced into the cisterna magna; KCl injections were subsequently injected via the same route. Before the KCl injections were made, the CSF initially withdrawn was reinjected and withdrawn a second time, in order to test the nonspecific effect of injecting any fluid intracisternally.

Blood and cerebrospinal fluid sodium, potassium and pH were determined by methods previously reported, using the process flame photometer and the Beckman Model G pH

*This work was aided by a grant from the U.S. Public Health Service (Grant H 141 C8).

Meter with sealed hypodermic type of glass electrode (Cooper, Lechner and Bellet[6]). Serum and CSF calcium was determined by the method of Clark and Collip[4].

CONTROL EXPERIMENTS (8 DOGS). The effects of intracisternal injections of KCl alone were recorded in dogs 1 to 8. These animals served as controls for the subsequent experiments. After baseline specimens and recordings were obtained, four concentrations of potassium chloride were injected intracisternally: 100 mEq./L., 500 mEq./L., 1000 mEq./L. and 2000 mEq./L. Two milliliters of each concentration respectively were injected at 15-minute intervals, with continuous recording of the electrocardiogram and blood pressure. The severity of muscular tremors which invariably resulted was also graded. Blood samples were obtained just prior to each injection and at the end of each experiment.

EFFECTS OF AUTONOMIC NERVOUS SYSTEM BLOCKING AGENTS (11 DOGS). The autonomic nervous system blocking agents were rapidly administered intravenously to dogs 9 to 13 and 15 immediately after the maximal blood pressure and electrocardiographic alterations were obtained by the intracisternal injection of 2 ml. KCl (500 mEq./L.). Phentolamine methanesulfonate (Regitine), 0.7 mg./kg. body weight was administered to dog 9, and 2 mg./kg. to dog 10. Hexamethonium chloride (1 mg./kg.) was administered to dogs 11, 12, 13 and 15. In dogs 16 to 20, the blocking agents were administered intravenously prior to the injection of KCl intracisternally. With dog 16 and 20, hexamethonium (2 mg./kg.) was administered intravenously and 30 minutes later KCl was injected intracisternally. Reserpine (Serpasil), 0.2 mg./kg. and 1 mg./kg. respectively, was administered intravenously to dogs 17 and 19 followed in 2 hours by KCl intracisternally. Phentolamine (3 mg./kg.) was administered intravenously 20 minutes before KCl was injected intracisternally in dog 18.

**Results.** EFFECT OF INTRACISTERNAL KCl ON THE ELECTROCARDIOGRAMS. The electrocardiographic disturbances were similar to those previously reported (Walker, Smolik and Gibson[20]), and ranged from a mild sinus tachycardia in dog 4 and mild slowing of ventricular rate in dog 6, to ventricular fibrillation in dog 3. Six of the 8 dogs of the "control" series, and all of the dogs which were given KCl intracisternally prior to giving sympathetic and parasympathetic blocking agents, developed various arrhythmias (Figs. 1 and 2). These consisted most frequently of bigeminy due to premature ventricular contractions, supraventricular tachycardias, nodal and idioventricular rhythms, ventricular tachycardia, multifocal ventricular premature contractions and ventricular fibrillation, in the approximate order of incidence. A slowing of the ventricular rate was frequently noted in conjunction with the initial blood pressure rise (Dogs 3, 5, 6, 8—Table 1) prior to the development of other arrhythmias. In no instances were arrhythmias noted without a change in blood pressure. The blood pressure on occasions rose without the development of arrhythmias (Dog 4, 6—Table 1). The critical height of blood pressure necessary for the development of arrhythmias varied from animal to animal, but ranged between 200 to 250 mm. Hg systolic.

EFFECT OF INTRACISTERNAL KCl ON BLOOD PRESSURE. The blood pressure increase after intracisternal KCl administration varied from as much as 270 mm. Hg systolic and 120 mm. Hg diastolic (for example, from a control value of 160/110 to 430/230 in dog 9—Table 2) to as little as 75 mm. Hg systolic and 60 mm. Hg diastolic (from 125/80 to 240/140 in dog 4—Table 1). The specific determinant of the degree of blood pressure rise and arrhythmia production in an individual dog could not be determined.

The blood pressure rise usually began 10 to 20 seconds after the 30 to 120 seconds necessary for the injected KCl to reach its maximal concentration. The blood pressure maintained this elevation for at least 5 to 10 minutes, and occasionally returned to baseline levels within 15 minutes. In no animal (without the use of blocking agents) was the blood pressure below 200 mm.

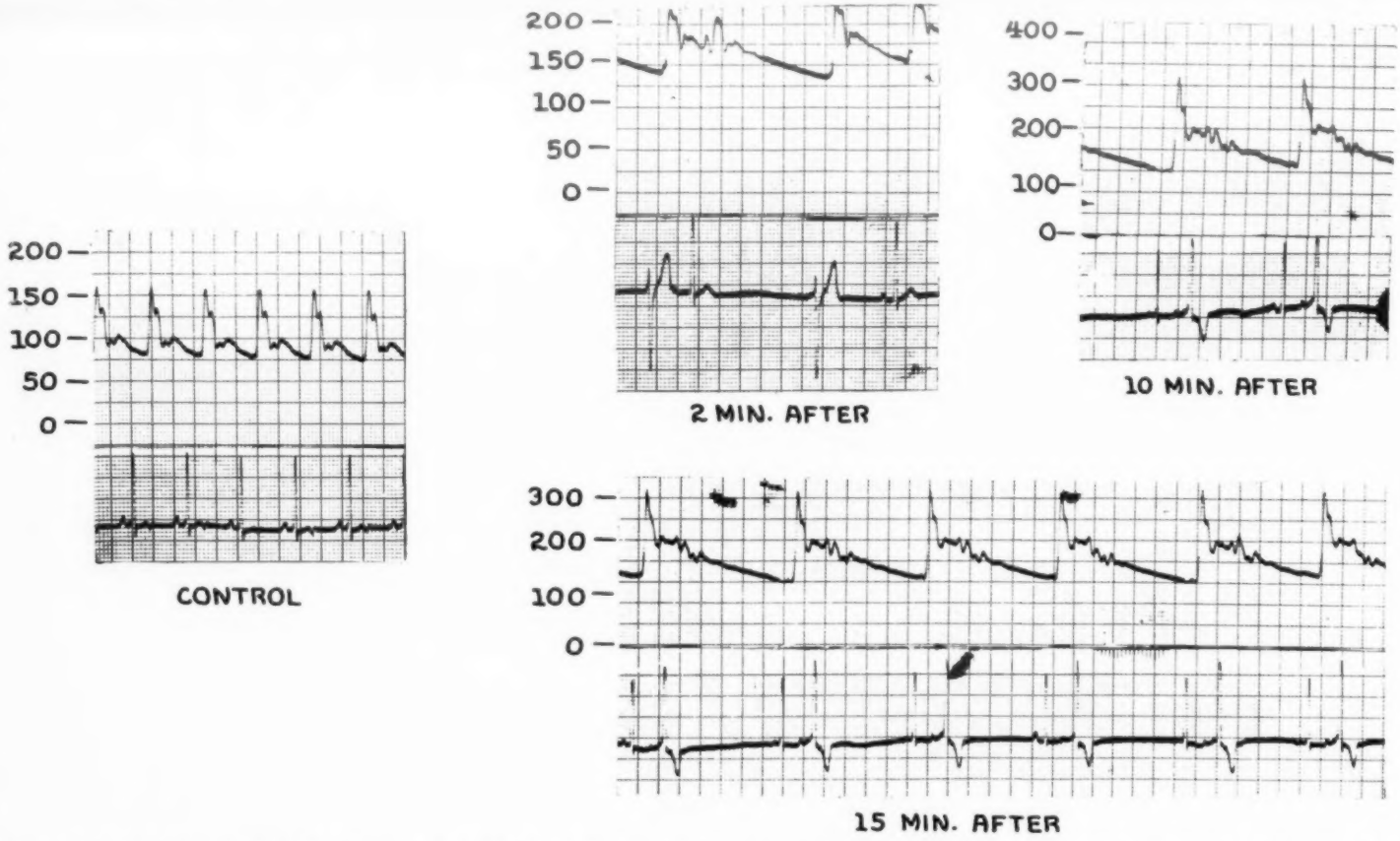


Fig. 1.°.—Dog 3—Two ml. KCl solution (100 mEq./L.) administered intracisternally. Blood pressure rose to 235/165 within 2 min. after the KCl intracisternal injection, with development of typical coupling which persisted for 15 min. Systolic pressure still above 300 mm. Hg 15 min. after injection.

°In this figure and all subsequent figures, blood pressure recordings are on top, ECG below. All blood pressure are recorded in millimeters Hg.

TABLE 1.—KCl INTRACISTERNALLY

| *Dog* | *Anesthesia* | *Drug Administered* | *Electrocardiogram* | *Blood Pressure* |
|---|---|---|---|---|
| 1 | Pentobarbital | 2 ml. KCl (100 mEq./L.) intracisternally | Marked sinus tachycardia (300/min.). High amplitude QRS with very tall T waves. | Not recorded |
| 2 | Pentobarbital | 2 ml. KCl (100-2000 mEq./L.) intracisternally | First, sinus tachycardia with prominent P waves and biphasic T waves. Then bigeminy due to premature ventricular contractions, followed by paroxysms of ventricular tachycardia. | Not recorded |
| 3 | Pentobarbital | 2 ml. KCl (100-2000 mEq/L.) intracisternally | After first injection, initial sinus bradycardia, later with PVC coupling. With second injection, ventricular tachycardia (or supraventricular tachycardia with aberration), followed by NSR as BP fell, finally ventricular fibrillation. | After first injection, BP rose from 180/110 to 235/165 in 2 min., then to 320/128 in 15 min. After second injection, further rise to 360/215, then fall to 0/0. No effect after subsequent injections. |
| 4 | Pentobarbital | 2 ml. KCl (100–2000 mEq./L.) intracisternally | Mild sinus tachycardia | Rose from 125/80 to 200/140 after first injection. No effect after subsequent injections. |
| 5 | Pentobarbital | 2 ml. KCl (100–2000 mEq./L.) | First injection, initial decreased ventricular rate, then marked RS-T segment ele- | After first injection, BP |

| | | | | |
|---|---|---|---|---|
| 5 | Pentobarbital | 2 ml. KCl (100–2000 mEq./L.) intracisternally | First injection, initial decreased ventricular rate, then marked RS-T segment elevation, then nodal tachycardia, with occasional PVC. After second injection, sinus tachycardia with very peaked P waves. | After first injection, BP rose from 110/75 to 190/125 in 30 sec. Then back up to 190/110 in 2.5 min. Still 190/100 15 min. later. Rose to 370/240 after second injection. BP. 250/175 five minutes later and 240/160 ten minutes later. No effect after subsequent injections. |
| 6 | Pentobarbital | 2 ml. KCl (100-2000 mEq./L.) intracisternally | No significant change, except slight fall in ventricular rate at height of BP rise. | After second injection, gradual rise to 205/155 in 105 sec. from a baseline of 110/75. Still 200/150 in 12 minutes. No effect after subsequent injections. |
| 7 | Thiopental | 2 ml. KCl (100-2000 mEq./L.) intracisternally | After first injection, wandering pacemaker followed by nodal and idioventricular rhythms, interrupted by PVC from low focus. Also, moderate RS-T segment depression and paroxysms of bigeminy (nodal rhythm with PVC) | After first injection, rise from 140/100 to 250/150. 200/135 seven min. after intracisternal KCl, and 190/130 ten min. after. Gradual rise to 210/130 after second injection. Slight effect after subsequent injections. |
| 8 | Thiopental | 2 ml. KCl (100-2000 mEq./L.) intracisternally | After first injection, rapid fall in ventricular rate from 190 to 110. Then periods of sinus pause and 2:1 A–V heart block, followed by coupling (PVC). Later multifocal PVC. After 2nd injection, a rapid ventricular tachycardia, followed by supraventricular tachycardia. | After first injection, immediate rise in BP from 155/115 to 380/200 remained for 10 min. After second injection rise from 250/150 to 400/275 within 15 sec. Slight effect after subsequent injections. |

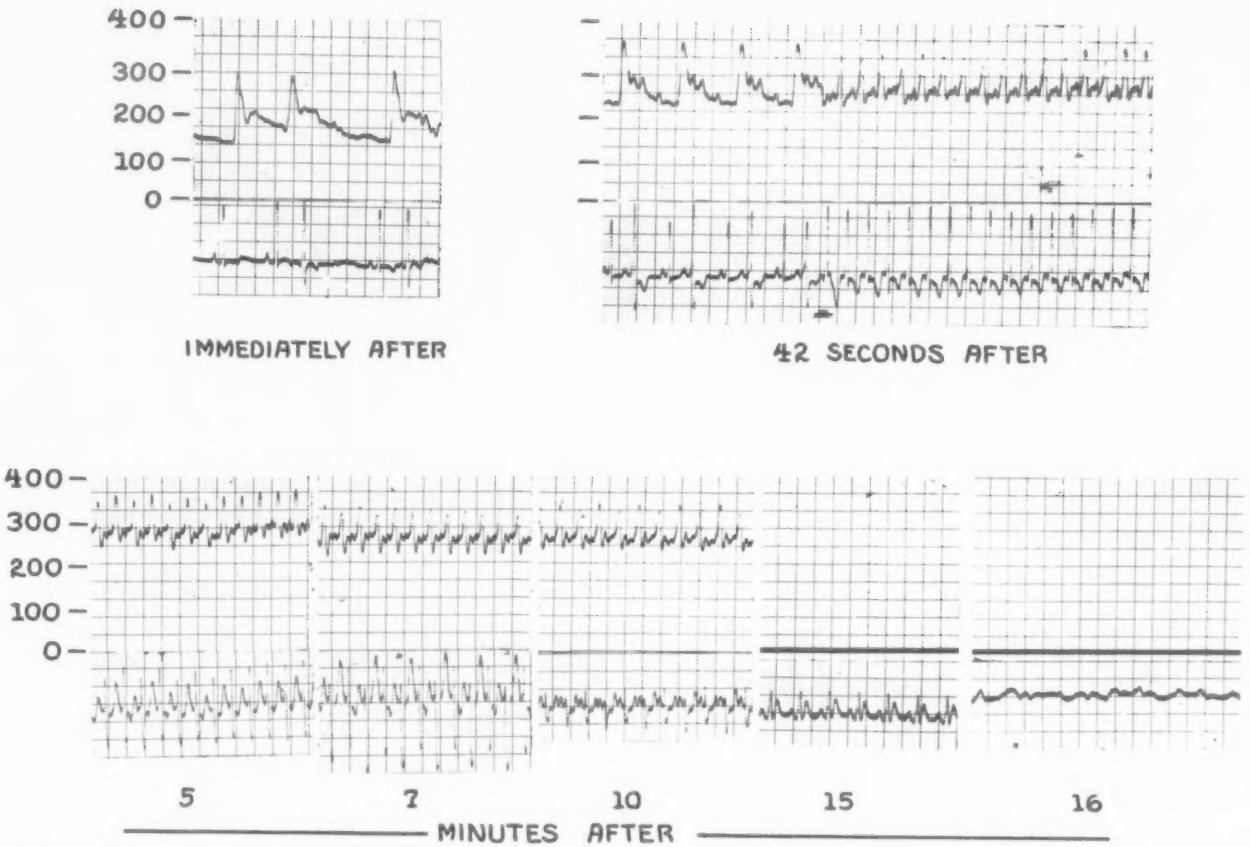


Fig. 2.—Dog 3—Two ml. KCl solution (500 mEq./L.) administered intracisternally. Note the very rapid tachycardia (either ventricular in origin, or supraventricular with aberration) which appeared 42 sec. after KCl injection, and persisted for 10 min. Shock eventually developed, and terminally ventricular fibrillation occurred.

Hg systolic within 5 minutes of intracisternal KCl administration. Following the initial 100 mEq./L. and 500 mEq./L. infusions, subsequent intracisternal injections usually produced no further significant change in the blood pressure, cardiac rate and rhythm. For example, infusion of the 1000 mEq./L. or 2000 mEq./L. KCl solutions had little or no effect when preceded by the lower concentrations of KCl.

EFFECT OF AUTONOMIC NERVOUS SYSTEM BLOCKING AGENTS. In dogs 9 to 20, sympathetic or parasympathetic blocking agents, or both were demonstrated to have very definite effects on the electrocardiographic and blood pressure changes seen after KCl intracisternal injections (Table 2). Their effects are summarized below:

*Regitine (3 dogs).* The blood pressure of dogs made acutely hypertensive by intracisternal KCl injections was lowered by phentolamine (Regitine) (0.7 mg./kg) when given intravenously, but it did not attain normal levels. For example, the blood pressure decreased from a level of 430/230 in dog 9 to 270/140 and 270/150 at 90 seconds and 5 minutes, respectively, after phentolamine intravenously. The hypertension in dog 10 responded to phentolamine (2 mg./kg.) by a drop to baseline levels within 70 seconds after intravenous administration, but the effect was only transient and the blood pressure later suddenly rose markedly and remained elevated for 15 minutes. Bigeminy due to premature ventricular contractions appeared for the first time in dog 10, eight seconds after phentolamine intravenously, and persisted for 19 seconds. In dog 18, phentolamine (3 mg./kg.) given intravenously immediately before KCl intracisternally caused no significant inhibitory effect on blood pressure or ECG changes.

*Hexamethonium (6 dogs).* Hexamethonium manifested a more definitive effect on the hypertension and arrhythmias in dogs 11, 12, 13, 15, 16 and 20 (Figs. 3 and 4). Hexamethonium produced a drop of blood pressure to below 200 mm. Hg systolic and 150 mm. Hg diastolic in all animals tested within 5 minutes of administration when given after KCl intracisternally. Such a drop had been noted in none of the "control" animals. In fact, baseline levels were reached in dogs 11, 12 and 15 within 125 seconds, 5 minutes and 2.5 minutes respectively, after intravenous hexamethonium. In dogs 11 and 12, bigeminy persisted for 20 seconds and 2.5 minutes, respectively, after baseline "normal" blood pressure levels had been obtained by intravenous hexamethonium. In dogs 16 and 20, intravenous hexamethonium given 30 minutes before KCl intracisternally prevented the usually marked blood pressure rise and arrhythmias observed with such KCl injections. The highest blood pressure recorded in these animals was 180/100 mm. Hg (30 seconds after KCl intracisternally in dog 20), and only occasional premature ventricular contractions were noted electrocardiographically. The severe muscular tremors which always developed after the intracisternal injection of KCl were of usual vigor in these latter animals in spite of minimal blood pressure change.

*Reserpine (2 dogs).* In dogs 17 and 19, reserpine in large doses (0.2 mg./kg. and 1 mg./kg. respectively), given intravenously 2 hours before KCl intracisternally, failed to prevent the marked hypertension and arrhythmias usually seen after such KCl injections (Fig. 5).

EFFECT OF MECHANICAL STIMULATION OF MEDULLA ON BLOOD PRESSURE AND ELECTROCARDIOGRAM. The medulla was inadvertently pricked in dogs 14 and 15 during the initial cisternal puncture

ventricular in origin, or supraventricular with aberration) which appeared 42 sec. after KCl injection, and persisted for 10 min. Shock eventually developed, and terminally ventricular fibrillation occurred.

TABLE 2.—SYMPATHETIC OR PARASYMPATHETIC BLOCKING AGENTS OR BOTH, WITH KCl INTRACISTERNALLY

| *Dog* | *Anesthesia* | *Drug Administered* | *Blood Pressure* | *ECG* |
|---|---|---|---|---|
| 9 | Thiopental | 2 ml. KCl (500 mEq./L.) intracisternally. Then phentolamine intravenously. | From initial of 160/110 began to rise 9 sec. after KCl intracisternally reaching a height of 430/230 in 45 sec. Phentolamine intravenously at that time caused BP fall to 270/140 within 90 sec. and 270/150 in 5 minutes. | Bigeminy due to PVC appeared in 15 sec. after KCl injection, later interrupted by one short paroxysm of ven. tachycardia. The coupling disappeared about 5 min. after phentolamine administration. |
| 10 | Thiopental | 2 ml. KCl (500 mEq./L.) intracisternally. Then phentolamine (2 mg./kg.) intravenously. | Rose to 300/210 from 220/165 within 1 min. after KCl intracisternally. Fell to baseline levels 70 sec. after phentolamine injection, then to 180/130. Suddenly rose to 275/190 and remained same for 15 min. | Bigeminy due to PVC appeared 8 sec. after phentolamine injection and lasted 19 sec. Otherwise, not remarkable. |
| 11 | Thiopental | 2 ml. KCl (500 mEq./L.) intracisternally. Then hexamethonium (1 mg./kg.) intravenously | Rose from 170/190 to 370/170 in 60 sec. after KCl intracisternally. After hexamethonium intravenously BP fell gradually back to baseline level (170/90) in 125 sec. | Bigeminy appeared 33 sec. after intracisternal KCl. After hexamethonium, I. V., bigeminy disappeared in 145 sec., 20 sec. after baseline BP level attained. |
| 12 | Thiopental | 2 ml. KCl (500 mEq./L.) intracisternally. Then hexamethonium (1 mg./kg.) intravenously | Rose from 130/75 to 390/240 in 48 sec. After hexamethonium, i.v., BP fell to 165/95 in 100 sec., and reached 136/70 in 5 minutes. | Sinus tachycardia-rate rose from 160 per minute to 220 within 5 sec. of KCl intracisternally. After hexamethonium, rate fell to 150 min. in 40 sec. |
| 13 | Thiopental | 2 ml. KCl (500 mEq./L.) intracisternally. Then hexamethonium (1 mg./kg.) intravenously | Rose from 110/60 to 380/240 in 40 sec. after KCl intracisternally. After hexamethonium i.v., BP fell to 190/140 in 5 min. and 170/120 in 7½ minutes. | Bigeminy due to PVC's, short runs of ventricular tachycardia and marked sinus tachycardia noted after KCl intracisternally. Arrhythmias disappeared 7½ mins. after hexamethonium i.v. |
| 14 | Thiopental | None | No significant change | Cisternal puncture alone produced EKG change (*See* Fig. 6). |

after hexamethonium i.v.

| | | | | |
|---|---|---|---|---|
| 14 | Thiopental | None | No significant change | Cisternal puncture alone produced EKG change (*See* Fig. 6). |
| 15 | Thiopental | KCl 2 ml. (500 mEq./L.) intracisternally. Then hexamethonium (1 mg./kg.) i.v. | Rapid marked rise on faulty reinjection of spinal fluid after cisternal tap (*See* Fig. 7). KCl intracisternally produced rise to 375/225 from baseline 180/115 in 125 sec. Hexamethonium resulted in fall of BP to baseline 180/115 in 2½ min. (5 min. after initial KCl injection). | Cisternal puncture and reinjection of spinal fluid produced EKG changes (*See* Fig. 7). |
| 16 | Thiopental | Hexamethonium (2 mg./kg.) i.v. Then 2 ml. KCl (500 mEq./L.) intracisternally. | No change after hexamethonium i.v. Little change after intracisternal KCl-(up from 100/50 to 130/65 in 1 minute and maximum rise to 170/110 in 2 min.). | I.V. hexamethonium induced T wave changes (from flat to inverted). Occasional PVC 2 minutes after KCl intracisternally. |
| 17 | Thiopental | Reserpine (0.2 mg./kg.) i.v. Then 2 ml. KCl (500 mEq./L.) intracistenally. | Rose from 90/40 to 350/200 within 45 sec. after KCl, in spite of reserpine. BP was 220/125 seven min. after KCl intracisternally, 260/170 ten min. after, and 230/160 fifteen min. after. | Heart rate slowed initially, then marked sinus tachycardia appeared. Runs of ventricular tachycardia appeared 7 min. after KCl intracisternally. |
| 18 | Thiopental | Phentolamine (3 mg./kg.) i.v. Then 2 ml. KCl (500 mEq./L.) intracisternally. | Rose from 100/60 to 325/190 by 67 sec. after KCl intracisternally, in spite of phentolamine. Five min. after KCl intracisternally, BP was 250/150. Ten min. after, BP was 185/120. | Occasional PVC noted after KCl intracisternally, occasionally occurring in pairs and triplets. |
| 19 | Thiopental | Reserpine (1 mg./kg.) i.v. Then 2 ml. KCl (500 mEq./L.) intracisternally. | Rose rapidly in spite of reserpine, reaching 310/150 by 15 sec. after KCl administration. BP was 230/80 five min. after KCl intracisternally, and 180/95 ten min. after. | Bigeminy appeared 12 sec. after KCl intracisternally. Bigeminy, interrupted by periods of marked sinus tachycardia, persisted for minutes. |

and removal of cisternal fluid. The prick was so minor that the cerebrospinal fluid did not become bloody. Yet, definite RS–T segment elevation with coving and terminal T wave inversion, and later bigeminy, appeared (Fig. 6 and 7). The cisternal fluid later was re-injected. A blood pressure rise to 390/180 mm. Hg (initial baseline was 180/115) was recorded in dog 15 after the re-injection of the cisternal fluid (probably caused by further medullary trauma) (Fig. 7). Routine removal and re-injection of cisternal fluid in the other animals caused no blood pressure or electrocardiographic changes.

EFFECT OF INTRACISTERNAL KCl ON SERUM ELECTROLYTES. No consistently abnormal serum electrolyte changes were noted during these experiments.

**Discussion.** Hypertension and cardiac arrhythmias thus can be produced with ease experimentally by electrical, mechanical and chemical (including asphyxia) stimulation of the brain stem of animals (1 to 11, 14 to 17, 21). Walker, Smolik and Gibson concluded that potassium phosphate given intracisternally produces a direct stimulating action on the medullary centers which activates sympathetic, vagal and respiratory mechanisms[20]. Potassium administered intracisternally easily perfuses into the brain substance (Rudolph and Olsen[17]), thereby reaching the apparently susceptible vasomotor centers of the medulla causing activation of these structures. Many of the vasomotor responses produced by the intracisternal injection of potassium salts can be counteracted and blocked by the intracisternal injection of calcium salts (Mullin, Hastings and Lees[13], Resnick *et al.*[16]).

Blood pressure changes and alterations of cardiac rate and rhythm were produced by mechanical (manipulative) and electrical stimulation in the region of the hypothalmus in humans who were undergoing neurosurgical procedures (White[24]). Unfortunately, electrocardiograms were not taken during these experiments, and therefore, the nature of the arrhythmias was not clarified.

It seems unlikely that such marked disturbances of the vasomotor centers can be produced so easily experimentally in animals and man, and their analogues not frequently be seen clinically in man. "Central" hypertension and cardiac arrhythmias are described clinically in man, but their true nature remains vague. Therapy of these states has consequently also remained vague. Clinicians have always suspected that the hypertension seen, for example, in bulbar poliomyelitis, brain tumors and with other central nervous system diseases is due to vasomotor center involvement. Cardiac arrhythmias are commonly seen in patients with cerebrovascular accidents. In the individual case, it is usually uncertain whether the arrhythmias develop before or after the accident.

Judging from the marked hypertension and frequency of bigeminy and tachycardia of various types which result when KCl is administered intracisternally, it is obvious that the sympathetic or vasoaccelerator center response is the dominant one. Bradycardia and A–V block occurred early in some of our animals, as well as an occasionally early slight decline in blood pressure (after an initial rise). These responses are manifestations of parasympathetic center activation, either from primary stimulation or from secondary reflex stimulation from peripheral pressor receptors. Regardless, it is not at all surprising that hexamethonium was most effective in preventing and ameliorating the vasomotor responses in these animals. Phentolamine, used in both adrenolytic and sympa-

tholytic doses, was only partially effective in controlling the hypertension resulting from KCl intracisternal administration. Reserpine was administered in large doses intravenously 2 hours before KCl was given intracisternally. Reserpine, apparently a hypothalamic depressor agent (Plummer *et al.*[14]), was completely ineffective in preventing blood pressure rises and arrhythmias. Perhaps this ineffectiveness of reserpine, in the face of medullary stimulation, is further proof of its hypothalamic rather than medullary site of




Fig. 3.—Dog 12—Two ml. KCl solution (500 mEq./L.) given intracisternally followed in 48 sec. by hexamethonium (1 mg./kg.) intravenously. *A*—Control. *B*—48 sec. after KCl intracisternally, just prior to I.V. hexamethonium. *C*—50 sec. after I.V. hexamethonium. *D*—100 sec. after I.V. hexamethonium. Note that I.V. hexamethonium, given after KCl intracisternally, reduced BP and heart rate promptly (within 100 sec.) to normal limits.




Fig. 4.—Dog 16—Hexamethonium (2 mg./kg.) administered intravenously, followed in 30 min. by 2 ml. KCl solution (500 mEq./L.) intracisternally. *A*—control. *B*—30 min after I.V. hexamethonium, just prior to KCl intracisternally. *C*—1 min. after KCl intracisternally *D*—2 min. after KCl intracisternally. *E*—5 min. after KCl intracisternally. Hexamethonium intravenously was able to almost completely prevent the hypertensive and arrhythmia-producing effects of the intracisternal KCl injection.

action. Also, reserpine is apparently unable to block the hypertension resulting from increased intracranial pressure, presumably because the hypertension results from vasomotor center (medullary) stimulation rather than hypothalamic stimulation (Trapold, Plummer and Yonkman[19]). The point of stimulation would, therefore, be "below" the site of reserpine action, and thereby account for its ineffectiveness.




Fig. 5.—Dog 17—Reserpine (0.2 mg./kg.) administered intravenously, followed in 2 hours by 2 ml. KCl solution (500 mEq./L.) intracisternally. *A*—Control. *B*—2 hours after reserpine I.V., just prior to KCl intracisternally. *C*—46 sec. after KCl intracisternally. *D*—7 min. after KCl intracisternally. Reserpine intravenously was ineffective in preventing the hypertensive and arrhythmia-producing effects in intracisternal KCl. Note the run of ventricular tachycardia (or supraventricular tachycardia with aberration) which appeared 7 min. after KCl intracisternally, causing a temporary fall in blood pressure.

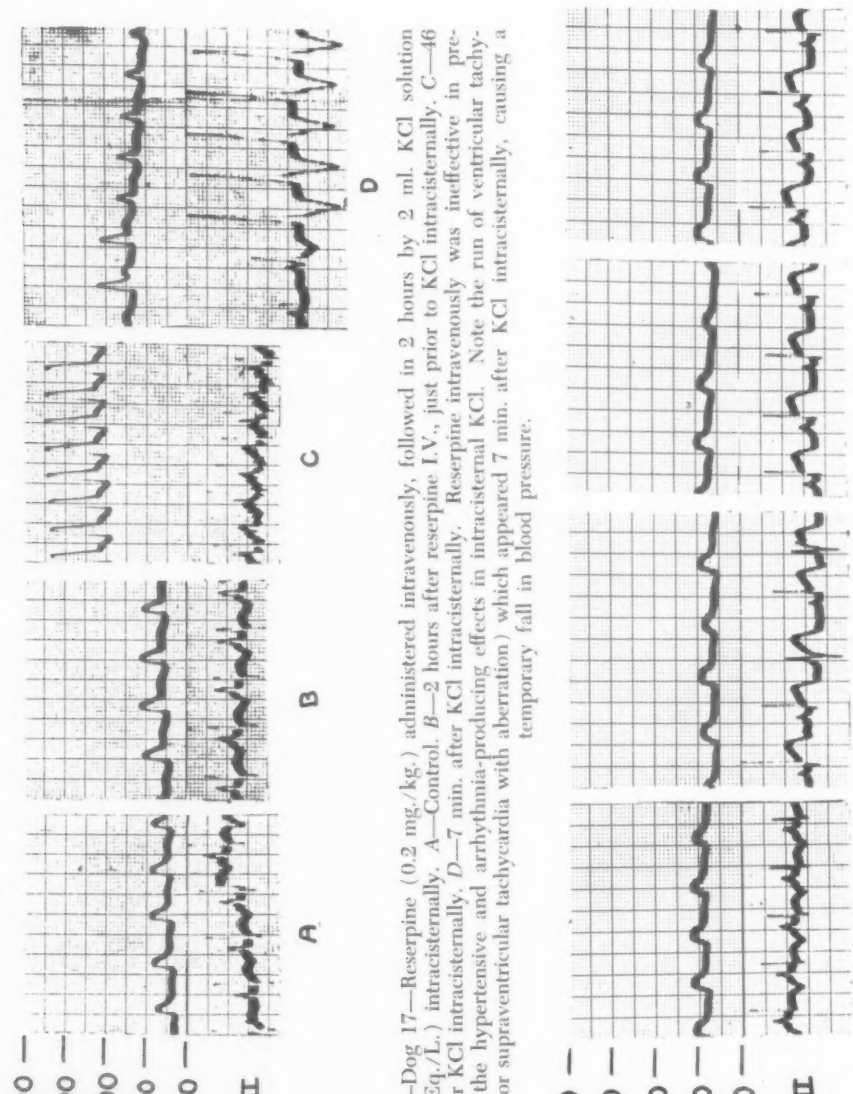


Fig. 6.—Dog 14—Changes resulting from inadvertent mechanical pricking of brain stem during cisternal puncture. *A*—Control. *B*.—Immediately after cisternal puncture. *C*—3 min. after cisternal puncture. *D*—15 min. after cisternal puncture. Note the rather marked RS–T segment elevation, simulating changes seen after direct myocardial injury. The RS–T segment elevation lasted 15 min.

Fig. 7.—Dog 15.—*A*—Control. *B*—Immediately after cisternal tap and removal of 4 ml. cisternal fluid. *C*— After reinjection of cisternal fluid. *D*—25 min. after reinjection of cisternal fluid. Removal of 4 ml. cisternal fluid after cisternal puncture produced T wave inversion and slight RS–T segment elevation. Upon reinjection of the cisternal fluid, the blood pressure rose suddenly and markedly, and runs of probable ventricular tachycardia appeared.

We have no good speculative answer as to what is the probable, usual stimulus or vasomotor activating factor in "central" hypertension in man. Perhaps, for example, local accumulation, in the region of the vasomotor center, of small amounts of potassium could occur during intracranial hemorrhage (especially when involving the brain stem) as the result of local hemolysis of erythrocytes or necrosis of surrounding nerve cells. Mechanical or asphyxial stimulation seems a more likely explanation under these circumstances, however. Regardless, it would seem that, preferably, a good ganglionic blocking

Fig. 6.—Dog 14.—Changes resulting from inadvertent mechanical pricking of brain stem during cisternal puncture. *A*—Control. *B*—Immediately after cisternal puncture. *C*—3 min. after cisternal puncture. *D*—15 min. after cisternal puncture. Note the rather marked RS–T segment elevation, simulating changes seen after direct myocardial injury. The RS–T segment elevation lasted 15 min.

agent such as hexamethonium would be effective therapy. There seems to be a growing awareness of the urgency of lowering the high blood pressure in patients with cerebral hemorrhage, not only to diminish the likelihood of further leakage from the ruptured cerebral vessel, but also to lessen the work load on an already damaged and perhaps failing heart. There seems to be little danger in producing cerebral thrombosis under these circumstances (Wright and Luckey[25]).

An interesting observation during these experiments was the ease with which even slight mechanical stimulation (needle prick) of the medulla could produce marked hypertension and cardiac arrhythmias. Elevation of RS–T segments and T wave coving and inversion, simulating those changes found in patients with myocardial infarctions, was produced by mechanical stimulation. Similar electrocardiographic changes have been reported following subarachnoid hemorrhage in humans (Wasserman *et al.*[22]). The exact mechanism by which these electrocardiographic changes are produced is not known. Sympathetic stimulation commonly produces T wave changes (Raab[15]), but not RS–T segment changes. This observation is being investigated further, and is to be the basis of a future report.

**Summary and Conclusions.** 1. Marked hypertension and a variety of cardiac arrhythmias were produced in dogs by the intracisternal injection of small quantities of potassium chloride solutions.

2. The cardiac arrhythmias produced consisted of bigeminy due to premature ventricular contractions, marked supraventricular tachycardias, nodal and idioventricular rhythms, ventricular tachycardia, multifocal ventricular premature contractions and ventricular fibrillation, in the approximate order of incidence.

3. The hypertension and cardiac arrhythmias produced in these experiments could most effectively be prevented and reversed by the use of hexamethonium. Phentolamine (Regitine) and reserpine were ineffective in this respect.

4. During the course of these experiments it was noticed that marked hypertension and varied cardiac arrhythmias could be produced by minor mechanical stimulation of the medulla. Also produced were RS–T and T wave changes closely resembling those seen in myocardial infarction and often seen in humans following subarachnoid hemorrhage.

5. Further clinical and experimental studies are necessary to determine the true nature and importance of hypertension and cardiac arrhythmias secondary to central nervous system disturbances.

ACKNOWLEDGMENT: We are indebted to Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for generous supplies of reserpine (Serpasil) and phentolamine methanesulfonate (Regitine), and to the Burroughs Wellcome Co., Tuckahoe, New York, for hexamethonium chloride (Hexameton).

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## SUMMARIO IN INTERLINGUA

### Effectos Cardiovascular Post Infusion Intracisternal De Chloruro De Kalium

1. Marcate grados de hypertension e un varietate de arrhythmias cardiac esseva evocate in canes per le infusion intracisternal de micre quantitates de un solution de chloruro de kalium.

2. Le arrhythmias cardiac assi evocate consisteva de bigeminia in consequentia de prematur contractiones ventricular, marcate tachycardias supraventricular, rhythmos nodal e idioventricular, tachycardia ventricular, multifocal contractiones ventricular prematur, e fibrillation ventricular—approximativemente in iste ordine de frequentia.

3. Le hypertension e le arrhythmias cardiac evocate in iste experimentos poteva esser prevenite o revertite le plus efficacemente per le uso de hexamethonium. Phentolamina (Regitina) e reserpina esseva sin effecto in iste respecto.

4. In le curso de iste experimentos, il esseva notate que marcate grados de hypertension e varie arrhythmias cardiac poteva esser evocate per minor intensitates de stimulation del medulla. Esseva etiam producite alterationes de RS–T, e de unda T, multo simile al alterationes vidite in infarcimento myocardial e frequentemente post hemorrhagia subarachnoide in humanos.

5. Plus extense studios clinic e experimental es necessari pro determinar le ver natura e importantia de hypertension e de arrhythmias cardiac occurrente secundari a disturbationes del systema nervose central.

# CLINICAL EXPERIENCES WITH TRIAMCINOLONE IN ELDERLY MEN

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In dealing with older people, the clinician often needs to employ an anti-inflammatory steroid in the face of existing or impending cardiac failure. In the past, this dilemma has not been easily solved. Practically all of the therapeutically useful corticoids exhibit an unwonted capacity for retaining sodium and water, as well as for producing many of the features of Cushing's syndrome.

In small laboratory animals, it has been shown that a congener of this group of compounds, triamcinolone*, possesses a rather high glucocorticoid and anti-inflammatory action (Bernstein and Feldman[2], Bernstein *et al.*[3], Dorfman, Rosenberg and Dorfman[8], Perrine *et al.*[31]), and a desirable sodium and water excreting effect (Bernstein and Feldman[2], Dorfman, Rosenberg and Dorfman[8], Paino *et al.*[30], Perrine *et al.*[31]). Because of this, the current observations with this new drug were begun in mid-summer, 1957, to determine (a) the presence or absence of sodium and water retention in older men; (b) the value of the drug in the clinical problems of older people; and (c) the nature and incidence of its side effects.

Clinical reports appearing since the present work was started have dealt with arthritis (Black, Yielding and Bunim[5], Di Raimondo and Forsham[7], Freyberg, Berntsen and Hellman[17], Hartung[21], Hellman *et al.*[22]), lupus erythematosus (Dubois[11,12], Spies[38]),

*Triamcinolone, chemically 9$_\alpha$-fluoro-11$_\beta$, 16$_\alpha$, 17$_\alpha$, 21-tetrahydroxy-1, 4-pregnadiene-3, 20-dione, or $\Delta^1$, 9$_\alpha$-fluoro-16$_\alpha$-hydroxy-hydrocortisone, was furnished for these studies by Lederle Laboratories under the trade name, Aristocort.

nephrosis (Hellman *et al.*[23]), various dermatologic (Hartung[21], Rein, Fleischmajer and Rosenthal[32], Sherwood and Cooke[36]), allergic conditions (Feinberg, Feinberg and Fisherman[15] Hampton[20], Schwartz[34], Sherwood and Cooke[36]), and congestive heart failure (Hampton[20]). In several of these reports, comparisons of triamcinolone with other anti-inflammatory steroids have been made, and its natriuretic and diuretic potency has been stressed (Di Raimondo and Forsham[7], Feinberg, Feinberg and Fisherman[15], Spies[38]).

**Methods and Procedure.** SUBJECTS. Thirty-one men, ranging in age from 35 to 75 with an average of 61.3 years, drawn from the wards of the Intermediate Service of this facility, were selected for the study because of the presence of edema, or of some condition which it was felt might be benefited by the use of a steroid of the 11-oxycorticoid type. The average weight of these subjects was 146.5 pounds with a range in weight from 93 to 231 pounds. Edema was initially present in 14 of the 31 individuals.

Treatment of one 44-year-old woman with psoriasis, not included in the electrolyte and water excretion studies, is also detailed because of its exceptional course and interest.

In a majority of the subjects there was a recognizable degree of "generalized" arteriosclerosis, sometimes more pronounced than might be expected from the chronological age.

The subjects were divided into two main groups for the purposes of the study: those with edema, of whom there were 14; and those without edema, of whom there were 18. The edema was associated with cardiac failure in 6 subjects; obesity in 2; chronic lymphedema, partly positional in origin, in 4 men; and cirrhosis in 2. Arteriosclerosis was a factor in all 6 instances of cardiac failure. The age of these subjects ranged from 57 to 75 years with an average of 65.8 years. Initially their weight averaged 166.7 pounds with a range of 101 to 231 pounds.

Of the subjects without edema, generalized arteriosclerosis was the only recognizable condition in 4. Other conditions in this group included rheumatoid arthritis in 5 individuals; osteoarthritis in 2; periarteritis nodosa, on the basis of clinical findings and biopsies, in 3 and chronic hypertrophic pulmonary emphysema, psoriasis, obesity and Huntington's chorea in one each. These subjects, exclusive of the psoriatic who did not participate in the metabolic studies, ranged in age from 35 to 70 years with an average of 56.2 years. Initially, their weight varied from 93 to 186 pounds with an average of 129.2 pounds.

DIET. In no instance was the dietary appreciably changed for the study, so that it is presumed the patient had been receiving approximately the same intake of food and fluid for at least 3 months prior to the use of triamcinolone. In the obese subjects, the caloric intake had been earlier limited to 1800 calories (carbohydrate, 180 gm.; protein, 80 gm.; and fat, 80 gm.) daily and was thus maintained throughout the study. In all other patients, the dietary was that routine for the wards; its approximate daily composition was carbohydrate 250 to 275 gm.; protein 70 to 80 gm.; and fat 85 to 95 gm. with a caloric value ranging from 2050 to 2275. The sodium content was calculated at around 110 ± 10 mEq. (2.5 gm.) daily. The only exceptions to this intake of sodium were 3 individuals with edema, in two of whom, with cardiac failure, sodium was restricted to 1.0 gm. (43.5 mEq.) and in the third with cirrhosis of the liver in whom dietary sodium was maintained at 500 mg. daily. Water consumption was not restricted.

LABORATORY METHODS. Sodium and potassium in serum and urine were determined by flame photometry (Beckman[1]). The estimation of urinary 17-ketosteroids was made according to the method of Drekter and associates[9,10]. Urinary adrenocorticoids of the 11-oxy type were determined by the method of Nowaczynski, Goldner and Genest[29] following hydrolysis with beta-glycuronidase and extraction of corticosteroids with chloroform (Glenn and Nelson[18]). Serum chloride was estimated by the procedure of Whitehorn[41] and carbon dioxide combining power according to the plan of Van Slyke and Cullen[40].

DOSAGE OF TRIAMCINOLONE. For all of the studies of water and electrolyte excretion a single level of dosage of triamcinolone was used, namely, 4 mg. three times daily. In purely clinical studies, which are continuing, the smallest effective daily dose has been 2 mg. three times daily, and the largest dose employed has been 4 mg. four times daily.

**Results.** In the recording of clinical and laboratory observations, comparisons will be made between those subjects with and those without edema. The nature of the problems of the in-

dividual subjects has already been described under **Methods and Procedure** (q.v.).

All urinary determinations were carried out on 24-hour aliquots repeated not less than 5 times prior to the use of triamcinolone, and not less than three times weekly during the periods of study and recovery, respectively. Periods of therapy varied from 5 to 151 days with an average of 59 days. Laboratory data were obtained over periods of time extending from 4 to 70 days with an average of 24.5 days.

LABORATORY DATA. *1. Water and Electrolyte Excretion Studies.* In Table 1, are recorded values for age, weight and urinary volumes and electrolytes in patients with and without edema. The former group is further subdivided into those receiving daily an average (110 mEq.) ration of sodium and those receiving 500 or 1000 mg. or less (that is, 43.5 mEq. or less). Under the influence of triamcinolone, weight loss was greatest in the edematous subjects for whom salt intake was restricted.

(a) URINARY VOLUME. In the control period, urinary volume was less for the edematous patients than for those who were edema-free (Table 1). In the respective periods, the differences in the several values between those with and those without edema were not tested statistically, as the underlying conditions were by no means comparable. However, in each group the differences in the values for urinary volumes before and after treatment as compared with the period of therapy were statistically significant (Table 1).

(b) SODIUM AND POTASSIUM EXCRETION. The excretion of both sodium and potassium was augmented during the administration of triamcinolone with a return to previous or lesser values following the discontinuance of the steroid (Table 1). The figures in Table 1 have been obtained by averaging all of the values for the stated period; before, during and after treatment, respectively. This, of course, does not show the whole picture. Maximal excretion was obtained in all instances shortly after beginning therapy. Later a "wearing off" effect could be observed, as is illustrated in Case A.L., Fig. 1. In this subject, a sodium deficit (Urinary output minus oral intake) of approximately 831 mEq. occurred. However, during this period a loss of 14 pounds of weight (6.4 kg.) took place. If calculated as sodium in terms of extracellular fluid, which, as Elkinton and Danowski[14] have commented, is a "questionable assumption," the loss is 890 mEq. It is obvious that the loss of weight represents more than a loss of sodium and water. During the same period of time serum sodium decreased from 142 to 138 mEq. per liter. Simultaneously the patient was for the first time in many months completely edema-free in both pulmonary and dependent portions of the body.

As a rule, in the edema-free subjects, intake and excretion returned to balance within 15 days of beginning treatment, while in those subjects with edema, balance was re-established some 3 weeks after triamcinolone was begun. However, in the latter group such a balance was not usually struck until maximal relief of edema had been obtained. This did not occur until the 70th day in one individual, although on the average it was present by the 19th day. At the other extreme, 2 individuals without edema showed their maximal excretion of sodium on the fourth day of treatment with return to figures approximating the intake by the seventh and ninth days respectively.

That the alterations in sodium excretion represented a new balance, rather than the "tiring out" of some renal or other mechanism is indicated

TABLE 1.—THE INFLUENCE OF TRIAMCINOLONE ADMINISTRATION ON THE WEIGHT AND ON THE URINARY VOLUME, NA, K AND 17-KETOSTEROIDS OF MEN WITH AND WITHOUT EDEMA

TABLE 1.—THE INFLUENCE OF TRIAMCINOLONE ADMINISTRATION ON THE WEIGHT AND ON THE URINARY VOLUME, NA, K AND 17-KETOSTEROIDS OF MEN WITH AND WITHOUT EDEMA

| | *14 Subjects With Edema* | | | | | | *17 Subjects Without Edema* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *All Subjects* | | | *Subjects On An Average Sodium Diet (2.5 gm.)* | | | | | |
| | *Units* | *% of Control†* | *P Value* | *Units* | *% of Control* | *P Value* | *Units* | *% of Control* | *P Value* |
| **WEIGHT** (lbs.) | | | | | | | | | |
| Beginning | 167 | 100.0 | | 175 | 100 | | 129 | 100 | |
| End | 155 | 92.9 | | 164 | 93.4 | | 127 | 98.4 | |
| **URINE**—Daily Values | | | | | | | | | |
| (a) Volume (ml.) | | | | | | | | | |
| Before | 859 | 100 | | 801 | 100 | | 1236 | 100 | |
| During | 1656 | 193 | <0.01 | 1900 | 237 | <0.01 | 1517 | 123 | <0.01 |
| After | 1164† | 135 | <0.05 | 1164* | 145 | <0.01 | 1285 | 194 | <0.05 |
| (b) Sodium (mEq.) | | | | | | | | | |
| Before | 81 | 100 | | 107 | 100 | | 102 | 100 | |
| During | 116 | 143 | <0.05 | 132 | 123 | <0.05 | 129 | 127 | <0.02 |
| After | 83* | 102 | <0.01 | 83* | 78 | <0.01 | 106 | 103 | >0.1 |
| (c) Potassium (mEq.) | | | | | | | | | |
| Before | 52 | 100 | | 57 | 100 | | 46 | 100 | |
| During | 62 | 120 | >0.1 | 66 | 115 | >0.1 | 58 | 126 | <0.05 |
| After | 54* | 104 | <0.05 | 54* | 95 | >0.1 | 41 | 89 | <0.01 |
| (d) NA/K | | | | | | | | | |
| Before | 1.56 | 100 | | 1.87 | 100 | | 2.06 | 100 | |
| During | 1.96 | 126 | | 2.00 | 107 | | 2.47 | 123 | |
| After | 1.58 | 101 | | 1.54 | 82 | | 2.65 | 132 | |
| (e) 17 KS (mg.) | | | | | | | | | |
| Before | 4.93 | 100 | | | | | 7.75 | 100 | |
| During | 4.04 | 82 | <0.05 | | | | 5.52 | 71 | <0.02 |
| After | 6.01 | 116 | <0.05 | | | | 6.03 | 78 | <0.01 |

*In none of the 3 subjects with low salt diet were determinations made after treatment was stopped.
†This refers to the % of the averaged value of all determinations in the control period of this study.

by the behavior of the case illustrated in Fig. 1. After becoming edema-free on the 21st day of treatment and remaining in sodium balance for an additional 18 days, the intake of sodium for this patient was raised from 45 to 110 mEq. daily with a prompt increase in excretion.

a trend towards higher values in all subjects during treatment.

Sodium and potassium ratios were calculated but revealed no significant trends (Table 1).

2. *Urinary 17-ketosteroid Excretion and 11-oxycorticoid Excretion.* In the group of patients with and that without

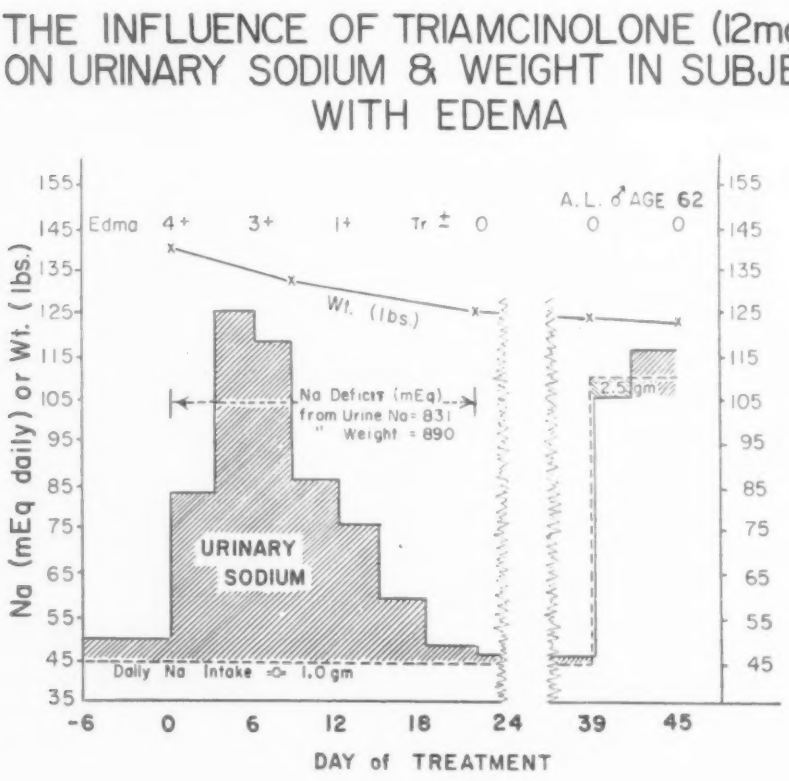


Fig. 1

In the present study, no attempt was made to calculate the intake of potassium. However, when the urinary values for this cation are compared with the figures recorded during treatment there is a statistically significant increase in association with the administration of the steroid to the subjects who had no edema (Table 1) and edema, there was a significant decrease in urinary 17-ketosteroid excretion well within the 5% level of confidence (Table 1). It was not possible to carry out the determination of 11-oxycorticoids in all patients, but for the limited number in whom completed no trends in relation to therapy were apparent.

3. *Serum Electrolytes and Carbon*

*Dioxide Combining Power.* Serum determinations of sodium, potassium, chloride and carbon dioxide combining power were carried out in each subject from one to four times during the "fore" or control period; from one to eighteen times during the period of administration of triamcinolone; and from one to four times during the "after" or "recovery" period. Averaged data recorded in Table 2 showed no significant alterations in any of these three periods.

TABLE 2.—AVERAGED VALUES FOR SERUM ELECTROLYTES AND CARBON DIOXIDE COMBINING POWER IN 31 PATIENTS BEFORE, DURING AND AFTER RECEIVING TRIAMCINOLONE.

| | *Value in mEq. or Millimols per Liter* | | | | | |
|---|---|---|---|---|---|---|
| | *Edema Initially (14 Subjects)* | | | *Without Edema (17 Subjects)* | | |
| *Serum Constituent* | *Before Treatment* | *During Treatment* | *After Treatment* | *Before Treatment* | *During Treatment* | *After Treatment* |
| Sodium | 140 | 138 | 139 | 139 | 140 | 139 |
| Potassium | 5.0 | 4.6 | 4.2 | 4.2 | 4.6 | 4.5 |
| Chloride | 100 | 99 | 100 | 99 | 99 | 96 |
| Carbon Dioxide Combining Power | 25 | 28 | 27 | 27 | 29 | 27 |

CLINICAL DATA. While taking triamcinolone, all of the 32 patients in the present study were observed for changes in their clinical condition, particularly for alterations in appetite, weight, edema, blood pressure, mental status, and symptoms of diseases commonly grouped together as amenable to therapy with steroids of the 11-oxycorticoid type. Care was taken to note and record undesirable manifestations, such as those of a Cushing's type not infrequently complicating therapy with "adrenocortical" steroids.

(a) *Appetite.* In 4 subjects, each underweight for his height and age, there was an improvement in appetite while under treatment with triamcinolone. In 2 of these, who suffered from rheumatoid arthritis, this could have been secondary to the relief of pain obtained by the use of the steroid. One of the others suffered from a mild osteoarthritis with moderate easily tolerated pain. In the fourth subject, advanced pulmonary fibrosis with secondary heart disease was the primary diagnosis. The last mentioned man's condition had remained more or less stationary for one year prior to the use of triamcinolone. Despite his loss of edema, he simultaneously gained weight and is now participating in activities previously denied him. Neither of the last 2 mentioned patients was subjectively aware of an improvement in appetite, but while taking triamcinolone their consumption of food has been definitely observed to increase.

For the remaining subjects, no real change in appetite has been recognized, although 2 of the 3 obese men in the present study believed it was easier for them to follow a diet restricted in calories, while taking the steroid.

(b) *Weight.* All but one of the 14 subjects, who initially showed some degree of edema, lost weight during the period of observation on triamcinolone. In the one exception, the weight did not change during 23 days of treatment. Of the 17 patients without edema initially, 4 who gained weight have been discussed above in relation to

appetite. Five neither gained nor lost, and the remaining 8 showed slight losses.

For the entire group of 31 patients there was a total weight loss of 200 pounds, or an average of 6.5 pounds per subject. For the subjects with edema initially the average loss was 11.7 pounds, and for those with no evidence of edema, the average decrease was 2.1 pounds. For the two groups these decreases represented 7.1 and 1.6%, of total average weight, respectively (Table 1).

(c) *Edema.* Edema was graded from 0 to 4 plus depending upon the surface area involved, the depth of pitting and the severity of lymph stasis. On this basis, 4 patients presented with 1 plus edema; 5 with 2 plus; 4 with 3 plus and 1 with 4 plus.

In 7 individuals the edema completely disappeared and, in 4, decreased to "a trace" while treatment with triamcinolone was administered. The edema of one severe cirrhotic increased while treatment with triamcinolone was being given. In a second individual with hepatic damage, the edema was unchanged by therapy. In the remaining subject, the edema diminished from 2 plus to 1 plus while triamcinolone was used.

(d) *Mental Status.* In one patient with widespread periarteritis, probably directly involving the brain, doses of 12 mg. of triamcinolone daily were associated with euphoria. This was in sharp contrast to the previously detached apathetic state of this individual.

(e) *Blood Pressure.* Blood pressures were taken on all patients at least three times weekly throughout the period of observation. No changes occurred which were attributable to the use of triamcinolone.

(f) *Daily Dosage and Duration of Treatment.* In Table 3 are contained the levels of dosage used, the number of subjects employing each level of dosage and the range and duration of treatment at that level, as well as the number transferred to a higher or lower level of dosage.

When 6 mg. of triamcinolone were used, 6 of the 7 subjects were unable to detect any relief of the manifestations for which prescribed. In the seventh, a long standing eczema of both legs was slightly improved, but not completely relieved until 8 mg. daily were employed.

TABLE 3.—LEVELS OF DOSAGE, LENGTH OF TREATMENT AND UNDESIRABLE EFFECTS IN 31 PATIENTS GIVEN TRIAMCINOLONE

| *Daily Dose* (*mg.*) | *No. Subjects* | *No. Days Treated* | | *No. Needing Doses Increased To* | | | | *Undesired Effects* | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Range* | *Average* | *8 mg.* | *10 mg.* | *12 mg.* | *16 mg.* | *No.* | *Type of Reaction* |
| 6 | 7 | 5–14 | 9.4 | 2 | 2 | 3 | 0 | 0 | |
| 8 | 6 | 5–56 | 24.8 | 0 | 0 | 2 | 1 | 0 | |
| 10 | 4 | 54–126 | 98.8 | 0 | 0 | 0 | 0 | 0 | |
| 12 | 23 | 9–151 | 54.6 | 0 | 0 | 0 | 0 | 6 | Pulmonary edema —1<br>Pulmonary congestion —1<br>Muscular weakness—2<br>Mooning of face —1<br>Purpura —1 |
| 16 | 1 | | 14 | – | – | – | – | 1 | Purpura—1 (?) |
| TOTALS | 41* | 5–151 | 59 | 2 | 2 | 5 | 1 | 7 | |

*This total fails to correspond to the total of 31 patients as several individuals were treated at more than one level of dosage.

Two of the 6 subjects given 8 mg. of triamcinolone daily were transferred to a dose of 12 mg. daily before an appreciable amelioration of their symptoms was observed. Three of the remaining 4 individuals obtained major to complete relief of symptoms at the 8 mg. level of dosage. One patient with chronic eczematous lymphedema of both legs was not relieved at any level of dosage. He developed purpura after 14 days of treatment with 16 mg. daily. The drug was immediately stopped; within 10 days his eczema, lymphedema and accompanying pruritus were better than they had been for several years.

Doses of 10 and 12 mg. daily of triamcinolone were usually accompanied by some evidence of pharmacological action, whether or not fully indicated for treatment of the condition prevailing in the individual subject.

(g) *Over-all Results of Treatment.* The over-all results of treatment are summarized in Table 4. Some comments on each of the conditions seem apropos.

TABLE 4.—RESULTS OF TREATMENT WITH TRIAMCINOLONE

| *Clinical Condition* | *No. Cases* | *Degree of Relief of Symptoms* | | | *Remarks* |
|---|---|---|---|---|---|
| | | *None* | *Partial* | *Complete* | |
| Generalized arteriosclerosis | 4 | 4 | 0 | 0 | No specific manifestations for which given. |
| Arteriosclerotic heart disease with rt. failure | 4 | 0 | 3 | 1 | Edema chiefly affected. |
| Chronic hypertrophic pulmonary emphysema | 1 | 1 | 0 | 0 | |
| With rt. heart failure | 2 | 0 | 2 | 0 | Congestion partially relieved. |
| Positional edema | 2 | 0 | 1 | 1 | |
| With eczema | 2 | 1 | 0 | 1 | Caused purpura in one obese individual with secondary hepatic damage. |
| Obesity | 1 | 0 | 1 | 0 | Lost weight and vague muscular pains, but developed muscular weakness with no change in serum K. |
| With lymphedema | 2 | 1 | 1 | 0 | |
| Arthritis | | | | | |
| Rheumatoid | 5 | 0 | 3 | 2 | |
| Other | 2 | 0 | 1 | 1 | |
| Periarteritis nodosa | 3 | 1 | 2 | 0 | |
| Psoriasis | 1 | 0 | 0 | 1 | Lesions present since 1st year of life. All manifestations gone in 3 wks. on 8 mg. daily. Pigmented skin remains. |
| Huntington's chorea | 1 | 1 | 0 | 0 | |
| Hepatic cirrhosis | 2 | 2 | 0 | 0 | Both severe; both died, one with purpuric manifestations. |
| TOTALS | 32 | 11 | 14 | 7 | |

A. GENERALIZED ARTERIOSCLEROSIS. Four subjects with no specific disturbances, other than arteriosclerosis, were included in the study chiefly to determine the presence or absence of an influence of triamcinolone upon water and electrolyte balance. No clinically recognizable changes took place in any of them during the period of drug ad-

ministration, although sodium, potassium and water excretion were influenced as above described.

B. ARTERIOSCLEROTIC HEART DISEASE WITH RIGHT-SIDED FAILURE. In no instance was triamcinolone the only therapy employed in these cases of arteriosclerotic heart disease with congestive failure. However, it was the only alteration made in therapy at the time the present observations were carried out. In 2 of the 4 subjects, previously existing peripheral edema and basilar pulmonary edema were completely relieved, while in the other 2 these were reduced. Weight was lost by each of the 4 subjects, and one patient became completely free of all cardiac manifestations. It should be particularly emphasized that this drug does not represent full therapy for any cardiac, but certainly appears to act synergistically with other medications. Contrary to most of its steroidal congeners, it is not contraindicated in the presence of edema or in impending cardiac decompensation.

C. CHRONIC HYPERTROPHIC PULMONARY EMPHYSEMA. When chronic hypertrophic pulmonary emphysema is associated with embarrassment of the right side of the heart, triamcinolone appears to reduce the pulmonary and peripheral congestion as well as the dyspnea. In uncomplicated emphysema, in the dosages used for the periods of time employed, there was no apparent alteration in the condition.

D. POSITIONAL EDEMA. While all 4 of the men with positional edema were overweight, it was felt that relative inactivity, 2 confined to wheel chair a major portion of the time, and the others predominantly sedentary in habits, was the major factor in the dependent edema and the secondary eczematous changes. In the one patient recorded as obtaining no relief, there was actual aggravation of the eczematous areas. These spots first appeared at 3 weeks with a daily dose of 12 mg. of drug, and were further aggravated by the use of 16 mg. daily for one week. After the steroid was stopped, the purpuric spots cleared promptly with some over-all improvement in the long standing eczematoid condition. This relief was so definite in the patient's mind, that he asked to be returned to the use of the drug. A dose of 8 mg. daily has been well tolerated for a period of 4 weeks without any purpuric manifestations but neither the eczema nor the pruritus has been further relieved.

E. OBESITY WITH LYMPHEDEMA. The lymphedema of obesity is usually improved with modest to marked reductions in weight and, as a rule, disappears if weight is brought to normal. The average weight of the 3 individuals included in the obesity group was 201 pounds at the beginning and 184 pounds at the end of the study (average height, 67 inches). No one of these individuals had lost weight for 3 months prior to initiation of the study, despite the use of the same diet employed throughout the period of treatment with triamcinolone. All 3 lost weight while this drug was being given, and the lymphedema of 2 subjects improved although it did not entirely disappear. One patient is recorded as being unimproved despite a weight loss of 27 pounds during 72 days of treatment with 12 mg. daily. He was classified as unimproved because he complained of increasing weakness, and finally refused further medication.

F. ARTHRITIS. Each of the 7 patients with arthritis obtained some relief of active manifestations when using triamcinolone. Complete suppression of these occurred in 2 of the 5 subjects with rheumatoid arthritis and in 1 of the 2 with an osteoarthritis. In 2 instances, the patient was transferred

from prednisone to triamcinolone. In the first of these 8.0 mg. of the latter proved as effective a maintenance dose as 10 mg. of the former. In the second patient, 12 mg. of triamcinolone was as effective as 20 mg. of prednisone. One patient with severe deformity and a continuously active arthritic process for some years, was considerably underweight at the beginning of treatment (123 lbs., 68 in. tall), lost 2 pounds in the first 7 weeks of treatment, and had gained 6 pounds over the original weight by the end of the twenty-second week of triamcinolone ingestion. Another patient with severe rheumatoid arthritis, while taking 20 mg. of prednisone a day, developed widespread acne of the face, chest and upper back. Under treatment with triamcinolone, 12 mg. daily, all active lesions completely disappeared, and the skin became generally more clear. Major degrees of relief have been afforded patients with arthritis with no evidences of edema in a single individual.

G. PERIARTERITIS NODOSA. In the patient with periarteritis nodosa, whose euphoria was mentioned above, considerable improvement has accompanied the use of steroidal therapy during the past year. He has now employed therapy with triamcinolone for approximately 4 months. Improvement already begun with prednisone has been steady. One patient has responded poorly, if at all, to triamcinolone in daily doses of 12 mg., and the third individual is very much relieved of muscular, abdominal and pulmonary symptoms.

H. PSORIASIS. The psychic and emotional factors bearing on the condition of the psoriatic patient are such that any statement about the condition, particularly as regards a single patient, would seem to be utter folly. However, this patient is a nurse, well informed regarding her disease, which she has had "as long as I can remember." The entire scalp, both elbows, buttocks and knees, and several patchy areas on the trunk were severely involved with characteristic plaques. On 8 mg. of triamcinolone daily for one week, the patient stated that the improvement was "greater than I have ever had from any treatment;" no local treatment was given. Within 5 weeks, all of the lesions have disappeared and only brownish pigmentation of the skin remains over the affected areas. She states that she has never been free of active lesions before in her entire life. A single case must be accepted with caution but the result is more dramatic than we have ever before witnessed from any treatment, psychic or otherwise.

I. HUNTINGTON'S CHOREA. This patient was included in our study, partly because of his enthusiastic cooperation in the laboratory studies and partly because we have felt that steroidal therapy might be useful in checking the gliosis of unknown etiology, which occurs in this disease. No recognizable change for better or worse has been noted in this individual.

J. CIRRHOSIS OF THE LIVER WITH ASCITES. Both patients with this condition appear to have been made worse by the use of triamcinolone. In one individual, in addition to an over-all increase in the severity of his hepatic decompensation, purpuric spots appeared at first over both lower extremities and later over the abdominal wall. These receded but did not completely disappear upon stopping the drug.

*(h) Undesirable Effects of Triamcinolone (Table 3).* It is rarely possible to determine all of the unwonted actions of a drug during a therapeutic trial with a limited number of subjects. Sometimes such reactions may go unnoticed or be erroneously ascribed to some other factor bearing upon the patient's medical problem. In conjunction with

the physical condition of the older male subject in a chronic disease hospital with dosages of triamcinolone not exceeding 16 mg. daily, the following conditions were thought to be related to the influence of the drug:

(1) PURPURA. Purpuric spots appeared over the legs and abdomen of a severe cirrhotic, who died of his cirrhosis on the sixty-third day of treatment with triamcinolone. It is difficult to be certain that these lesions were due to the action of the steroid, as they are quite commonly seen terminally in patients with this disease. However, we have the impression that the cirrhotic state was aggravated by the use of triamcinolone, although a cause-effect relationship must still be held *sub judice*. That purpura was induced in one patient over areas of eczematous lymphedema by administering triamcinolone cannot be doubted, for they disappeared promptly when administration of the drug was stopped. In this individual no abnormal alteration of platelets or of clotting, bleeding and prothrombin times could be detected.

(2) EUPHORIA. Euphoria occurred in one patient with periarteritis, but this appeared to be a hopeful sign of improvement, rather than an indication of toxicity. No other alterations in mental status were observed in any subject.

(3) "CUSHING-LIKE" FEATURES. Except for "mooning" of the face in one individual, features of Cushing's syndrome, such as acne, hypertension, gastric complaints, and peripheral edema were not observed in the present group of subjects. Indeed, in two instances in which therapy with prednisone had been complicated by acne and peripheral edema, these cleared under treatment with triamcinolone in doses of 12 mg. daily.

(4) WEAKNESS. Weakness was a subjective symptom in one patient with obesity and in one with rheumatoid arthritis. In the first instance, it necessitated discontinuance of the drug. In the second, the manifestation disappeared while the drug was continued at the same level of dosage, 12 mg. daily. In neither instance was muscular weakness demonstrated by simple bedside tests, nor was serum potassium altered.

(5) "WITHDRAWAL" MANIFESTATIONS. Sudden withdrawal of triamcinolone, somewhat to our surprise, was not attended in any individual by the manifestations of adrenal insufficiency. However, a rather marked retention of fluid appeared in 3 subjects, who had received 12 mg. of the drug daily for 57, 31 and 52 days, respectively. One obese subject, who prior to medication with triamcinolone had had one plus edema of the legs, relieved during triamcinolone therapy, developed rapid re-accumulation of fluid in the same area 48 hours after discontinuing the use of the steroid. Two patients, relieved of mild congestive failure while taking triamcinolone, developed pulmonary edema, in one instance, acute, within 72 hours of discontinuing the drug. Caution against stopping the use of triamcinolone suddenly is indicated by the appearance of this "rebound phenomenon," particularly in those patients with potential or known cardiac failure.

**Discussion.** That triamcinolone bears the hallmark of adrenocortical steroids of the cortisone type is certain, as it acts vigorously upon protein, carbohydrate, water and electrolyte metabolism. However, from the present observations as well as those made by others (Bernstein and Feldman[2], Bernstein *et al.*[3], Black, Yielding and Bunim[5], Di Raimondo and Forsham[7], Dorfman, Rosenberg and Dorfman[8], Dubois[11,12], Feinberg, Feinberg and Fisherman[15], Freyberg, Berntsen and

Hellman[17], Gutner *et al.*[19], Hampton[20], Hartung[21], Hellman *et al.*[22,23], Hollander[24], Paino *et al.*[30], Perrine *et al.*[31], Rein, Fleischmajer and Rosenthal[32], Schwartz[34], Sherwood and Cooke[36], Spies[38]) it is clear that the compound has several distinctive features. Indeed, we believe this is true of all of the major compounds in this group which have been used clinically. In this connection, cortisone and hydrocortisone are very similar; prednisone and prednisolone are likewise pharmacologically close to each other. It now appears that triamcinolone and 6-methyl-prednisolone have many features in common (Di Raimondo and Forsham[7]). Di Raimondo and Forsham believe that these two compounds possess from 3 to 4 times the anti-inflammatory activity of hydrocortisone, while showing no retention of sodium[7]. The present study has been conducted chiefly to determine the applicability of triamcinolone to the problems of older patients in cardiac failure and to those with any form of edema, who may have need of an anti-inflammatory agent. Furthermore, the nature and intensity of its side effects have been recorded.

The present observations fully confirm those of other workers (Dorfman, Rosenberg and Dorfman[8], Feinberg, Feinberg and Fisherman[15], Freyberg, Berntsen and Hellman[17], Hartung[21], Hellman *et al.*[22], Paino *et al.*[30], Perrine *et al.*[31]) in regard to the rather marked excretion of water, sodium and, to the least extent, potassium under the influence of this drug at a daily level of dosage, insofar as our patients are concerned, of 12 mg.

In their communication, Feinberg, Feinberg and Fisherman call attention to the relief of edema of cardiac origin but note a failure to alter other types of edema[15]. In 12 of our 14 patients who initially had edema this was relieved, irrespective of cause. The edema developing as a result of therapy with other steroids has been reported to disappear while using triamcinolone (Di Raimondo and Forsham[7], Feinberg, Feinberg and Fisherman[15], Paino *et al.*[30] and Sherwood and Cooke[36]). Indeed, the use of triamcinolone and methylprednisolone seems never to have been associated with sodium retention, although this point needs further study.

In commenting upon the water and sodium excretion routinely attendant upon the use of triamcinolone, it must not be forgotten that under proper circumstances anyone of the six steroids already mentioned can produce some degree of natriuresis and hydriuresis (Di Raimondo and Forsham[7], Forsham and Thorn[16], Kinsell *et al.*[26], Laidlaw *et al.*[27], Skoog and Adams[37]). The nature of this diuresis seems still not to have been fully determined, although several mechanisms have been suggested (Birnie *et al.*[4], Earle *et al.*[13], Luetscher and Curtis[28], Seldin[35], Streeten, Pont and Conn[39]).

In the present series of cases the increase in water and sodium excretion accompanying the ingestion of triamcinolone has always been associated with an augmentation of urinary creatinine (Kao and McGavack[25]). Conn, Streeton and Pont[39] and Earle and his co-workers[13] observed the same phenomenon whenever hydrocortisone caused diuresis. They suggested that the greatly increased glomerular filtration rate caused by the steroid far outweighed the increased tubular reabsorption of sodium. The marked increase in urinary volume under the influence of triamcinolone in the present series of cases would lead us to believe that this is at least one factor in the increased excretion of sodium. Emphasis upon glomerular filtration as the cause of the diuresis accompany-

ing the action of triamcinolone and other corticoids does not preclude the simultaneous or independent influence of extra-renal factors (Birnie *et al.*[4], Forsham and Thorn[16], Luetscher and Curtis[28], Seldin[35]). Failure to observe reversal of natriuresis and hydriuresis in any of our patients during relatively long periods of observation may indicate a special use for this steroid in patients with severe cardiac disease, who simultaneously have some clear indication for the exhibition of its anti-inflammatory action.

In his discussion of prednisone, Riemer[33] has called attention to a sodium excreting action, which has proved synergistic to other therapy in patients with refractory cardiac edema. Whether prednisone can always be relied upon to act as it did in his case may still be a moot question. It is probably too early to decide whether or not triamcinolone will always promote the excretion of water and salt. However, such a monophasic action was the only type observed in our 31 patients. This leads us to believe that triamcinolone can be used with safety for patients in cardiac failure, at least in doses employed for the present study.

We believe potassium diuresis is a factor to be countered with in the use of triamcinolone, as it has continued up to 70 days in some of the subjects we have treated, with changes in excretion which are statistically significant. Nevertheless, in no instance have we seen any abnormal alteration in serum potassium. Other workers (Bunim, Black and Simon[6], Freyberg, Berntsen and Hellman[17], Hartung[21], Hellman *et al.*[22]) have seen neither hypokalemia nor a negative balance for potassium even though doses above those employed in the present study were used.

The only steroid of the 11-oxycorticoid group with which we have thus far compared triamcinolone is prednisone. In general, effective dosages of triamcinolone on a weight for weight basis have equalled those of prednisone or are somewhat less. It would seem that the dosage equivalents vary somewhat from disease to disease. For instance Rein, Fleischmajer and Rosenthal[32], in treating several types of dermatological conditions, found triamcinolone useful in 1/2 to 2/3 the effective dose observed for prednisolone. From a study of patients with various allergies, Feinberg, Feinberg and Fisherman[15] have concluded that the maintenance dose of triamcinolone is approximately 1/2 that of prednisone and 2/3 that for methylprednisolone. In treating bronchial asthma and allergic rhinitis, Sherwood and Cooke[36] found triamcinolone effective in 2/3 of the dose necessary for prednisone. From our own studies effective dosages seem to range from 8 mg. daily upward, the highest dosage we have used being 16 mg. Maintenance doses have ranged from 6 mg. upward.

The number of cases herewith reported warrants no discussion of the incidence or severity of side effects. However, we have gained the impression that severe hepatic damage may be a contraindication to the use of the drug. Features of Cushing's syndrome have been met less frequently than with other corticoids of this general type. Furthermore, some distressing manifestations have disappeared when a transfer of the patient from therapy with prednisone to triamcinolone has been effected.

**Summary.** 1. Triamcinolone has been administered to 31 men with an average age of 51.3 years and one woman whose age was 44 years.

2. Edema was present in 14 of the men and was secondary to cardiac failure in 6.

3. Under the influence of triamcinolone there was a significant loss of water, sodium and potassium in the 31 subjects tested over periods of time varying from 7 to 70 days. These losses were greatest in those persons who were initially edematous.

4. The edema was apparently not influenced in one person with severe cirrhosis of the liver, nor in a second individual with lymphedema and secondary eczema.

5. In the first days of treatment all subjects lost weight, but in 5 without edema there was later an increase in weight.

6. Urinary 17-ketosteroid excretion was depressed during treatment with triamcinolone.

7. The values for serum sodium, potassium, chloride, and $CO_2$ combining power were not appreciably altered by the use of triamcinolone.

8. Under treatment with triamcinolone, there was some improvement in appetite in 4 subjects; no recognizable change occurred in the others.

9. Euphoria was observed in one subject; this may have represented an improvement in the previous apathetic state.

10. Blood pressure was not appreciably altered by the use of triamcinolone.

11. In general, dosages between 6 and 12 mg. daily proved to be therapeutically effective in the observed conditions, which included lymphedema, edema due to cardiac failure, arthritis, periarteritis nodosa and psoriasis.

12. No clinically recognizable influence was exerted in patients with "uncomplicated" generalized arteriosclerosis, chronic hypertrophic pulmonary emphysema without heart failure, Huntington's chorea and hepatic cirrhosis. In fact, the last mentioned condition may have actually been aggravated.

13. Among the undesirable effects of triamcinolone in the present series of cases should be included purpura in 2 subjects; weakness in 2; mooning of the face in one. Upon withdrawal of the drug retention of fluid and probably also of sodium occurred in 3 individuals, one of whom developed acute pulmonary edema.

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## SUMMARIO IN INTERLINGUA

### Experientias Clinic Con Triamcinolona In Homines De Etate Avantiate

1. Triamcinolona esseva administrate a 31 masculos con un etate medie de 51,3 annos e a un feminina qui habeva 44 annos de etate.

2. Edema esseva presente in 14 del masculos. Illo esseva secundari a disfallimento cardiac in 6.

3. Sub le influentia de triamcinolona il occurreva un significative perdita de aqua, natrium, e kalium in le 31 subjectos testate durante varie periodos de inter 7 e 70 dies. Iste perdita esseva le plus grande in le subjectos qui esseva initialmente edematose.

4. Le edema esseva apparentemente non influentiate in un persona con sever cirrhosis de hepate, ni in un secunde persona con lymphedema e eczema secundari.

5. Durante le prime dies del tractamento, omne le subjectos monstrava un perdita de peso, sed in 5 sin edema il occurreva subsequentemente un augmento de peso.

6. Le excretion urinari de 17-cetosteroide esseva deprimite durante le tractamento con triamcinolona.

7. Le uso de triamcinolona non resultava in un alteration significative del valores de natrium, kalium, e chloruro del sero o del potentia del sero a combinar $CO_2$.

8. Durante le tractamento con triamcinolona, il occurreva un certe melioration del appetito in 4 subjectos. Nulle recognoscibile alteration esseva presente in le alteres.

9. Euphoria esseva observate in un subjecto. Isto representava possibilemente un melioration in le previe stato de apathia.

10. Le pression de sanguine non esseva alterate de maniera notabile per le uso de triamcinolona.

11. A generalmente parlar, doses de inter 6 e 12 mg per die se provava therapeuticamente efficace sub le conditiones observate. Istos includeva lymphedema, edema como resultato de disfallimento cardiac, arthritis, periarteritis nodose, e psoriasis.

12. Nulle clinicamente manifeste influentia esseva exercite in patientes con "non-complicate" arteriosclerosis generalisate, chronic emphysema pulmonar hypertrophic sin disfallimento cardiac, chorea de Huntington, e cirrhosis hepatic. De facto, il es possibile que le ultime del conditiones mentionate esseva plus tosto aggravate.

13. Inter le effectos adverse de triamcinolona in le presente serie de casos, on debe mentionar purpura in 2 subjectos, debilitate in 2, e "lunation" facial in un. Post cessation del administration del droga, retention de fluido e probabilemente etiam de natrium occurreva in 3 individuos. Un de istes disveloppava acute edema pulmonar.

# ANTIHYPERTENSIVE ACTION OF THE ANTIMICROBIAL AGENT FURAZOLIDONE

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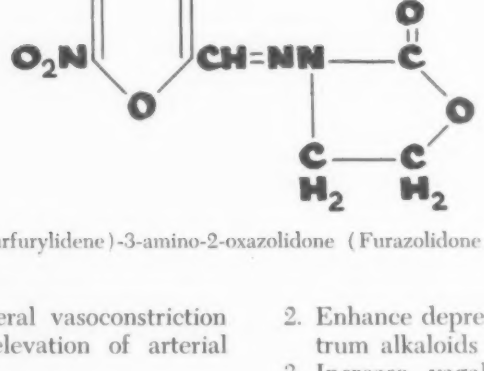
Primary hypertension comprises the majority of all cases of elevated diastolic and mean arterial blood pressure. Although the cause is obscure, the fundamental mechanism is an unbalanced autonomic nervous system with a resultant sympatheticotonia leading to peripheral vasoconstriction and consequent elevation of arterial blood pressure.

In the modern medical management of primary hypertension, the most widely used hypotensive drugs specifically decrease sympathetic tone by various methods:

1. Decrease sympathetic tone by anatomical blockades:
   a. cerebral cortex: depressants—barbiturates
   b. Subcortical: tranquilizers—Rauwolfia drugs (reserpine), meprobamate, and others
   c. Medulla: Veratrum alkaloids (alkavervir, protoveratrines)
   d. Autonomic ganglia: chlorisondamine, pentolinium, mecamylamine
   e. Effector cell: adrenolytic agents, phenoxybenzamine
2. Enhance depressor reflexes: Veratrum alkaloids
3. Increase vagal tone: Rauwolfia drugs and Veratrum alkaloids
4. Antagonize humoral substances (pressor amines): hydralazine
5. Relaxation of vessel walls: hydralazine

## STRUCTURAL FORMULA



N-(5-nitro-2-furfurylidene)-3-amino-2-oxazolidone (Furazolidone or Furoxone).

This article is a report on the antihypertensive action of furazolidone (Furoxone) which is a member of the nitrofuran series of antimicrobial compounds and has the chemical structure shown above.

None of the nitrofurans had be-n

found to have any effect on the cardiovascular or respiratory systems until Calesnick and DiPalma[3] first reported the hypotensive action of furazolidone while investigating the human pharmacology of this drug.

Furazolidone is a yellow crystalline solid which melts with decomposition at 255° C. It is stable under ordinary conditions but darkens if subjected to strong light for long periods of time. Like other nitrofurans, it is sensitive to the action of alkali. Its solubility in water is 40 mg. per L. at 25° C.

Furazolidone is bactericidal and highly effective both *in vitro* and *in vivo* against a wide variety of microorganisms (Yurchenco, Yurchenco and Piepoli[10]) by inhibiting microbial enzymatic metabolism (Rogers *et al.*[7]). The drug is used clinically as a topical trichomonacide and as a peroral enteric antibacterial agent, and also in veterinary medicine for various bacterial and protozoal infections of poultry.

Rapid catabolism of nitrofurans occurs when incubated with intestinal tissue, liver, kidney and skeletal muscle, starting by reductions of the 5-nitro group (Bender and Paul[2]). End-products isolated to date have shown no demonstrable antimicrobial activity. Nitrofurans reversibly inhibit the anaerobic formation of acetyl coenzyme A from pyruvate (Paul *et al.*[6]). Aerobically, nitrofurans (specifically nitrofurazone) act as inhibitors in the xanthine oxidase-hypoxanthine system (Taylor, Paul and Paul[9]). Continuous intravenous infusion of furazolidone solution into dogs fails to elicit a vasomotor response.

Following peroral administration of furazolidone to normal individuals, 0 to 9% appears in the feces and 2 to 8% in the urine, which may be tinted from deep yellow to brown. The blood level is from 0.9 to 3.3 μg. per ml. No drug can be detected chemically in the cerebrospinal fluid. The blood pressure of normotensives is unaltered.

**Methods and Results.** The present series of subjects was studied thoroughly to determine the effectiveness as well as the mode of action of furazolidone. Initially they were screened by the following studies in order to evaluate their hypertensive status: Body weight, systolic and diastolic blood pressures, pulse, eye grounds, complete blood count, sedimentation rate, urinalysis, blood urea nitrogen, blood sugar (postprandial), liver function tests (alkaline phosphatase, thymol turbidity and flocculation, bilirubin and transaminases), electrocardiogram, electroencephalogram, intravenous urogram, regitine test and the Funkenstein test. Both the electrocardiogram and eye grounds in many patients revealed changes indicative of elevated diastolic pressure of long duration. After this screening program, 16 subjects, all diagnosed as having uncomplicated primary hypertension were selected. A majority of them was ambulatory (10), the others (6) being hospitalized. No attempt was made to restrict either their salt or caloric intake. These hypertensives were observed at weekly intervals at which time all essential data were recorded.

Preliminary testing in several individuals (Figs. 1 and 2) illustrated clearly the hypotensive effect of furazolidone. One patient prematurely ran out of medication at the end of the 10th week and both systolic and diastolic pressures immediately began to rise (Fig. 2). She came to our laboratory the following (11th) week at which time she was placed on placebo.

In subsequent studies, all subjects were started on a daily peroral dosage of 800 mg. (200 mg. 4 times a day) which was reduced gradually (Figs. 3, 4 and 5) when the hypotensive response became stabilized. Table 1

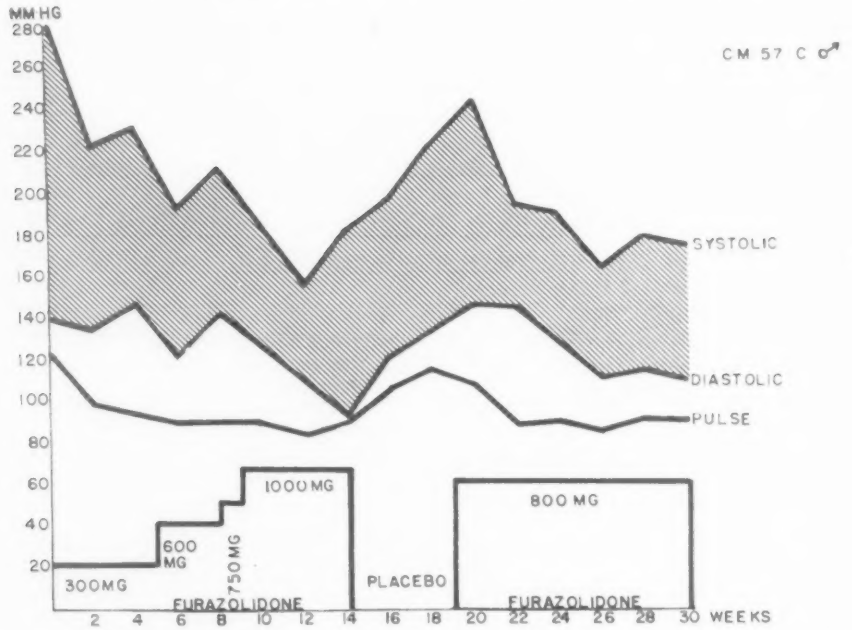



Fig. 1.—Initial steppage dosage of furazolidone revealed a hypotensive response. After 5 weeks of placebo, a repeated course of drug therapy again reduced both systolic and diastolic blood pressure. A bradycardia was also produced.

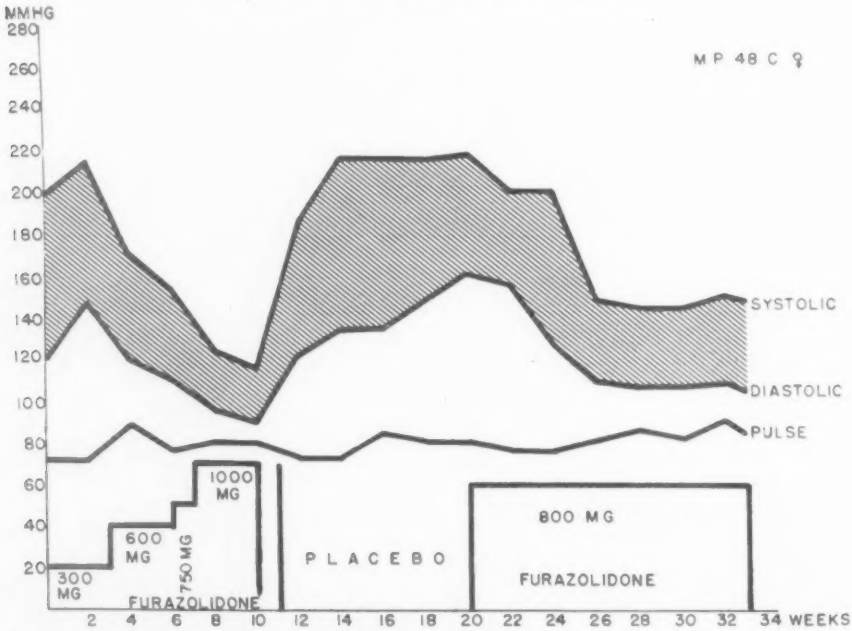



Fig. 2.—This patient ran out of medication at the end of the 10th week and returned to the laboratory the following week. She was placed on a placebo and arterial blood pressure rose to the pretreatment level. Another course of furazolidone again reduced the blood pressure in 6 weeks.

TABLE I.—PERTINENT DATA ON PATIENTS STUDIED

| Patient | Age | Color | Sex | Before Treatment | | Weeks Required for Hypotensive Response | After Treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | B. P. (sitting) | Pulse | | B.P. | | | Pulse |
| | | | | | | | Supine | Sitting | Standing | |
| C.B. | 59 | W | F | 192/112 | 93 | 5 | 148/90 | 134/84 | 136/86 | 87 |
| E.B. | 65 | C | F | 198/120 | 96 | 4 | 136/80 | 120/74 | 110/68 | 79 |
| E.B. | 48 | W | F | 204/126 | 99 | 3 | 175/106 | 162/98 | 150/104 | 75 |
| K.B. | 68 | W | M | 202/100 | 81 | 2 | 138/86 | 136/82 | 132/92 | 78 |
| C.C. | 68 | W | F | 220/100 | 66 | 8 | 146/80 | 148/76 | 142/78 | 72 |
| C.F. | 45 | W | M | 180/110 | 87 | 4 | 166/86 | 160/80 | 154/78 | 84 |
| C.F. | 42 | W | M | 226/124 | 96 | 2 | 144/94 | 140/90 | 142/92 | 86 |
| E.F. | 62 | W | F | 216/108 | 68 | 2 | 162/84 | 160/84 | 156/80 | 90 |
| F.H. | 54 | C | F | 158/110 | 90 | 2 | 146/96 | 148/98 | 158/102 | 84 |
| M.H. | 40 | C | F | 168/128 | 66 | 7 | 118/92 | 116/90 | 108/82 | 68 |
| M.K. | 43 | W | F | 218/116 | 86 | 3 | 168/120 | 158/106 | 154/112 | 69 |
| C.M. | 57 | C | M | 280/140 | 129 | 6 | 180/108 | 162/104 | 150/90 | 86 |
| R.M. | 62 | W | F | 226/116 | 75 | 8 | 176/92 | 152/76 | 140/84 | 84 |
| M.P. | 48 | C | F | 200/120 | 72 | 8 | 122/96 | 124/96 | 118/94 | 80 |
| C.R. | 59 | W | M | 174/94 | 60 | 5 | 140/80 | 110/75 | 105/70 | 72 |
| K.W. | 59 | C | M | 182/122 | 90 | 2 | 148/102 | 148/104 | 146/102 | 84 |

shows that in this group, the reduction in arterial blood pressure occurred between the second and eighth week, with no subjective or objective evidence of orthostatic hypotension. The effect of furazolidone on the calculated mean arterial blood pressure (Table 2) was recorded and the average reduction was 39 ± 12 mm. Hg.

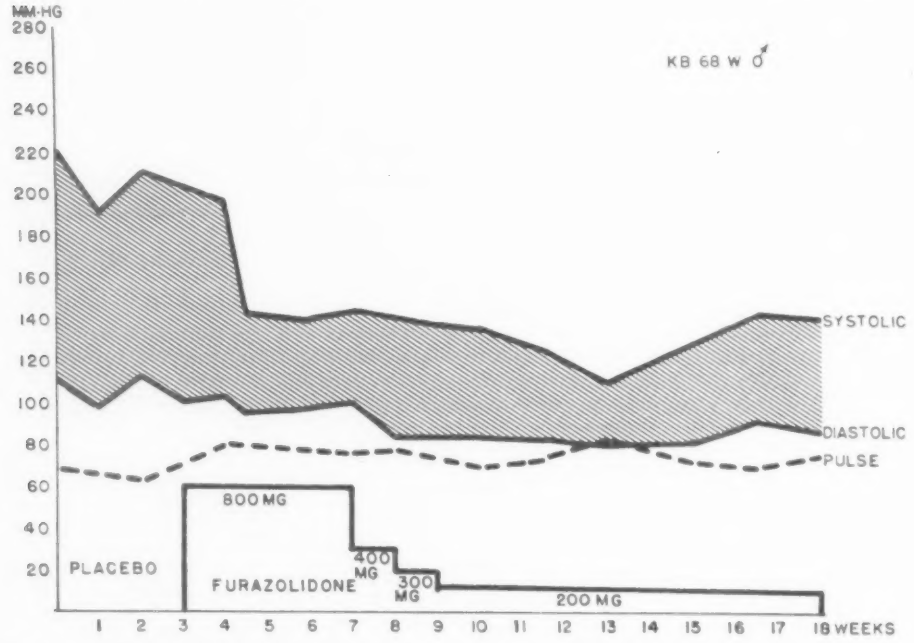



Fig. 3.—The reduction in arterial blood pressure was maintained with only ¼ the initial dose of 800 mg. a day. No tolerance was observed.

Various approaches were used to determine the basic factor(s) involved in this hypotensive response.

A. Bacteriological studies of the intestinal flora were made as follows: Each patient had 2 stool cultures performed before, during and at the peak of the reduction of blood pressure. No gross changes were observed qualitatively or quantitatively using aerobic and anaerobic or eosin-methylene-blue agar plates techniques (Table 3).

B. Blood volume determinations were carried out in 3 cases (Table 4). It is of interest that not only was no change observed in the blood volumes, but all values were within the norm of this laboratory.

C. Using the $Na^{22}$ method, the sodium space and exchangeable sodium were determined (Table 5) revealing an increase in sodium excretion with a decrease in both calculated sodium space and total exchangeable sodium. There was no significant change in either serum sodium or potassium.

D. Study of protein-bound iodine was performed to show the status of the thyroid function (Fig. 5). Again no significant change was observed.

E. Electroencephalographic studies also revealed no change from the control patterns.

F. Because of the chemical similarity of this nitrofuran to certain anticonvul-

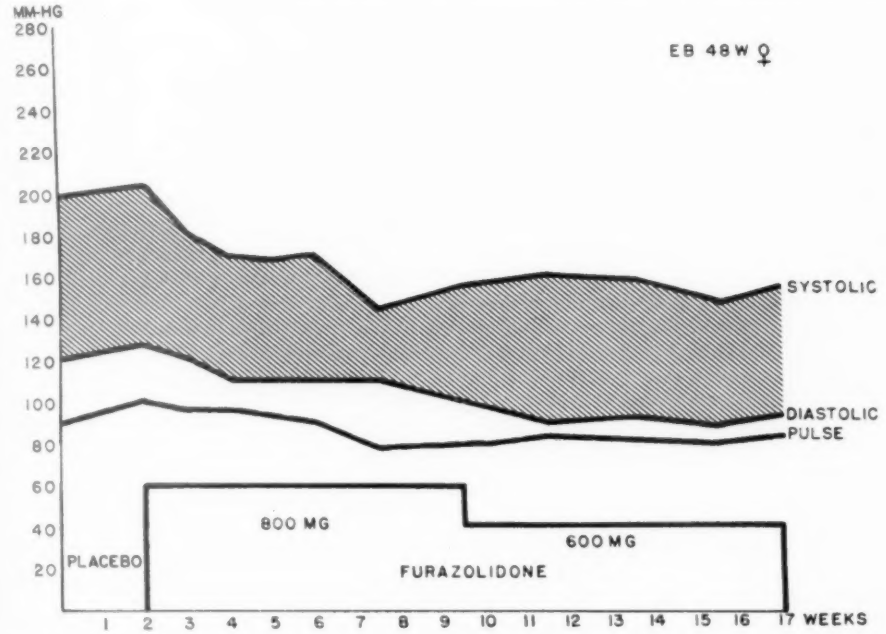



Fig. 4.—Arterial blood pressure was reduced after a period of 4 weeks' medication. There was no evidence of tolerance with a reduction in dosage.

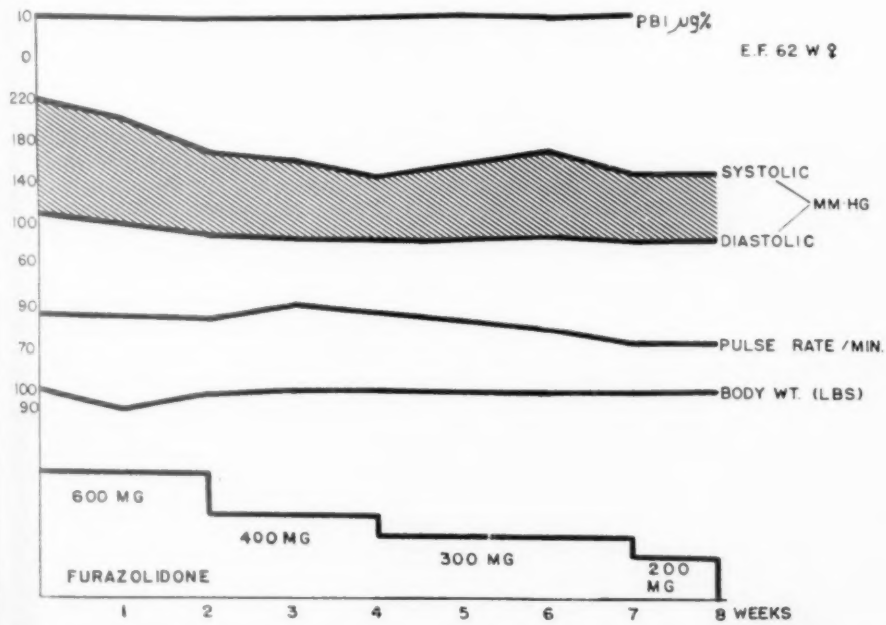



Fig. 5.—Principal effect was a reduction in systolic blood pressure. No change in protein-bound iodine was observed. Slight initial weight loss was due to nausea which disappeared with continuous medication.

sants (trimethadione) the effect of furazolidone on the electroconvulsion threshold was measured on rabbits. No perceptible changes were observed.

The main side effect of furazolidone was nausea, but after 2 to 4 weeks of continuous treatment this diminished or disappeared and the drug was better tolerated. Nausea could be controlled with prochlorperazine, suggesting that the gastrointestinal disturbance may have a central component in the chemoceptive trigger zone. However, in many cases aluminum hydroxide alone was sufficient to modify this gastrointestinal disturbance.

Normocytic anemia of the primaquine type, as has been reported in a few Negroes with nitrofurantoin (Kimbro, Sachs and Torbert[5]), was de-

TABLE 2.—MEAN ARTERIAL BLOOD PRESSURE (SITTING)

| *Patient* | *Initial Control* | *Furazolidone Response* | *Difference* |
|---|---|---|---|
| C.B. | 139 | 101 | 38 |
| E.B. | 146 | 89 | 57 |
| E.B. | 152 | 119 | 33 |
| K.B. | 134 | 100 | 34 |
| C.C. | 140 | 100 | 40 |
| C.F. | 133 | 107 | 26 |
| C.F. | 158 | 107 | 51 |
| E.F. | 144 | 109 | 35 |
| F.H. | 136 | 114 | 22 |
| M.H. | 141 | 99 | 42 |
| M.K. | 150 | 122 | 28 |
| C.M. | 187 | 123 | 64 |
| R.M. | 153 | 101 | 52 |
| M.P. | 147 | 105 | 42 |
| C.R. | 121 | 87 | 34 |
| J.W. | 142 | 119 | 23 |
| | | Average 39 ± 12* | |

*Standard Deviation

TABLE 3.—EFFECT OF FURAZOLIDONE ON INTESTINAL FLORA

| | | |
|---|---|---|
| *Before Therapy* | | |
| *Aerobic* | *Anaerobic* | *Eosin Methylene Blue* |
| *E. coli* | Non-hemolytic Streptococcus sp. | *E. coli* |
| *Staphylococcus aureus* | Pseudomonas sp. | *Proteus vulgaris* |
| Non-hemolytic Streptococcus sp. | Clostridium sp. | Non-lactose fermenters |
| Pseudomonas sp. | | |
| Fungi | | |
| *After Therapy* | | |
| *E. coli* | Non-hemolytic Streptococcus sp. | *E. coli* |
| *Staphylococcus aureus* | *E. coli* | *Proteus vulgaris* |
| Pseudomonas sp. | | Non-lactose fermenters |
| *B. subtilis* | | |
| *Proteus vulgaris* | | |
| Clostridium sp. | | |
| Enterococci | | |

tected also in several of our Negro patients, but was not seen in the Caucasian subjects.

A brownish discoloration of the urine, presumably due to the presence of small amounts of the drug and its metabolites, was noted during therapy. None of the subjects complained of this chromaturia, which was useful as evidence that the drug was being ingested, especially in the management of ambulatory patients.

TABLE 4.—BLOOD VOLUME DETERMINATION (INTRAVENOUS RADIOACTIVE IODINATED HUMAN SERUM ALBUMIN METHOD)

| *Patient* | *Calculated Total* Plasma Volume* | *Calculated† Blood Volume* | *Total Packed‡ Red Cell Volume* | *Hematocrit* |
|---|---|---|---|---|
| *C.M.* | | | | |
| 1 | 33 ml./kg. | 60 ml./kg. | 27 ml./kg. | 46.6% |
| 2 | 34 | 59 | — | — |
| *R.M.* | | | | |
| 1 | 39 | 68 | 29 | 46.7 |
| 2 | 42 | 70 | 28 | 42.9 |
| *E.B.* | | | | |
| 1 | 36 | 64 | 28 | 47.8 |
| 2 | 35 | 63 | 28 | 48.2 |

1 = Control
2 = Hypotensive response
Established normal values for this laboratory:
* = 35 to 45 ml./kg.
† = 65 to 85 ml./kg.
‡ = 30 to 40 ml./kg.

An unusual reaction occurred in 1 patient (C.F.) who took some beer while on furazolidone and within 10 minutes complained of facial flushing, lacrimation, conjunctivitis, weakness and light-headedness. This is similar to the symptoms produced by alcohol in an individual sensitized by disulfiram. This occurred every time he drank beer, the reaction persisting for 20 to 45 minutes.

**Discussion.** In an attempt to explain the mechanism whereby furazolidone decreases the elevated arterial blood pressure of primary hypertension, several important features must be emphasized. First, the blood pressure of normotensives is unaltered. Second, there is a gradual reduction to a stable plateau which cannot be lowered farther by increased doses so that orthostatic hypotension does not occur. Up to 8 weeks of continuous medication may be required to produce this effect. Furthermore, once this reduced pressure level is obtained it is stable and the dosage can be gradually reduced without affecting it.

If furazolidone acts by decreasing sympathetic tonicity, the following hypotheses should be considered:

1. Although the intestinal flora is not grossly changed, the possibility remains that certain intestinal organisms which liberate pressor amines are eliminated.

2. Biotransformation of the nitrofuran may result in the formation of a compound capable of producing para-

TABLE 5.—TOTAL EXCHANGEABLE SODIUM ($NA^{22}$ METHOD)

| *Patient* | *Total Counts Injected* | *Total Counts Excreted (24 hrs.)* | *Calculated Total Sodium Space* | *Calculated Total Exchange Sodium* | *Serum Sodium* | *Serum Potassium* |
|---|---|---|---|---|---|---|
| *C.M.* | | | | | | |
| 1 | $36.7 \times 10^6$ | $1.15 \times 10^6$ | 565 ml./kg. | 75.2 mEq./kg. | 134 mEq. | 6.4 mEq. |
| 2 | $31.5 \times 10^6$ | $2.36 \times 10^6$ | 469 | 63.7 | 139 | 6.4 |
| *R.M.* | | | | | | |
| 1 | $28.0 \times 10^6$ | $1.69 \times 10^6$ | 505 | 72.7 | 144 | 5.5 |
| 2 | $26.4 \times 10^6$ | $2.92 \times 10^6$ | 183 | 25.4 | 139 | 6.4 |
| *E.B.* | | | | | | |
| 1 | $28.6 \times 10^6$ | $0.45 \times 10^6$ | 230 | 34.5 | 141 | 4.7 |
| 2 | $23.0 \times 10^6$ | $1.26 \times 10^6$ | 217 | 30.5 | 150 | 4.5 |

1 = Control

2 = Hypotensive response

sympatheticotonia. A survey of the chemical structures of various cholinergic agents reveals that pilocarpine, muscarine and furtrethonium all contain the furan nucleus.

Schroder[8] showed that in essential hypertension, carbohydrate metabolism is altered. Gitelson[4] found that in severe stress, including hypertension, there is an elevation of blood pyruvic acid which may be the result of pituitary-adrenal discharge. Extensive *in vitro* studies have demonstrated that certain nitrofurans (nitrofurazone) inhibit the anaerobic formation of acetyl coenzyme A from pyruvate. In resting bacterial cell suspensions, nitrofurazone also impairs enzymatic dehydrogenation systems involved in carbohydrate metabolism, as shown by its marked inhibition of the aerobic oxidation of glucose, pyruvate, succinate, glycerol and lactate, and of the anaerobic dissimilation of pyruvate, glucose and formate (Asnis and Gots[1]). The classical disulfiram reaction in one of our patients suggests that furazolidone may also inhibit *in vivo* the enzyme system responsible for the conversion of acetaldehyde to acetate. The interruption of various metabolic pathways of carbohydrate metabolism may give us a clue as to its hypotensive action.

The result of prolonged metabolic studies indicates a decrease in total exchangeable sodium space and an increase in renal excretion of sodium without alteration of serum sodium and potassium. The observations require further study since no change was observed in blood volume.

To consider simply this vasodepressor action a function of the nitro group, as found in the organic nitrates, is not warranted at this time since continuous intravenous infusion of furazolidone into dogs failed to elicite a vasomotor response.

**Summary.** It has been demonstrated empirically that when furazolidone is administered by mouth there is produced a slow, gradual reduction of arterial blood pressure in patients with primary hypertension. The time required for this response varies between 2 to 8 weeks. This drug is poorly absorbed from the intestinal tract and the systemic toxicity is minimal. Although the mode of action is still under investigation, several possible mechanisms have been discussed.

ACKNOWLEDGMENTS: I am indebted to Eaton Laboratories, Norwich, New York, for a financial grant and supply of the antimicrobial agent, furazolidone; to Dr. A. Bondi, Jr., from our Division of Microbiology for the bacteriological studies; and to Dr. Millard N. Croll, from our Department of Radiology, for the isotope studies.

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## SUMMARIO IN INTERLINGUA

### Le Action Antihypertensive Del Agente Antimicrobial Furazolidon

Esseva demonstrate empiricamente que le administration oral de furazolidon resulta in un lente e gradual reduction del pression de sanguine arterial in patientes con hypertension primari. Le tempore requirite pro iste responsa varia inter 2 e 8 septimanas. Le droga es mal absorbite per le vias intestinal, e su toxicitate systemic es minimal. Le modo de su action es ancora sub investigation, sed plure possibilitates es discutite.

# NECROPSY EVALUATION OF THE GAS CONTRAST ROENTGEN VISUALIZATION OF LIVER AND SPLEEN

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The gas contrast Roentgen visualization of liver and spleen[7] has been in use at this hospital since 1948, well over one thousand such examinations having been performed without mishap. Our staff has learned to rely upon this simple procedure for more accurate appraisal of liver and spleen size than is possible at the bedside (Zelman and Pickard[8]). Serial visualizations have served to follow the progress of disease involving gross changes in these organs.

The stomach is distended with gas by ingestion of Seidlitz powders, and the colon is inflated with air by rectal tube and bulb, after which Roentgen exposures are made with the patient erect. In this position, the gas in the colon rises to outline the lower borders of liver and spleen. The medial borders are outlined by gas in the stomach, or, in the case of the laterally positioned spleen (Zelman[7]), by the splenic flexure of the colon. A postero-anterior exposure best reveals the liver, and a left anterior oblique exposure at approximately 30 degrees of obliquity best reveals the spleen, though good visualizations of both organs are usually obtained in each of the 2 views.

A review of necropsies performed at this hospital since introduction of the gas contrast Roentgen visualization of liver and spleen revealed 20 cases in which the procedure had been carried out within 3 months of death. Nine of these were done in the last month of life. Measurements of the Roentgen shadows of liver and spleen of these 20 cases were compared with weights of the organs recorded at necropsy. As a comparative standard, Roentgen measurements of the heart were obtained in a similar number of patients who came to necropsy at comparable intervals after their chest roentgenograms had been obtained, and these were compared with weights of the heart.

The Roentgen shadow of each organ was measured in 2 diameters, designated L (length) and W (width). Measurements of the liver were taken from the postero-anterior film made at 40 inch distance (Fig. 1). The "length" L was measured from the lower right edge to the highest point of the upper border. The "width" W was measured from the costophrenic angle to the midpoint of the lower border. These are the measurements used by Pfahler[5], except that the costophrenic angle is substituted for the "highest point of the right lobe" in the interest of greater precision. Of the 20 cases, measurements of the liver of one could not be made because of poor visualization.

The spleen shadow in the left anterior oblique view was used for measurement, L and W representing the largest obtainable straight line diameters at right angles to each other (Fig. 2).

For the heart, the well known long and broad diameters were used (Fig. 3), the long diameter extending from the junction of the cardiac and vascular silhouettes on the upper part of the right border obliquely downward to the apex on the left, the broad diam-

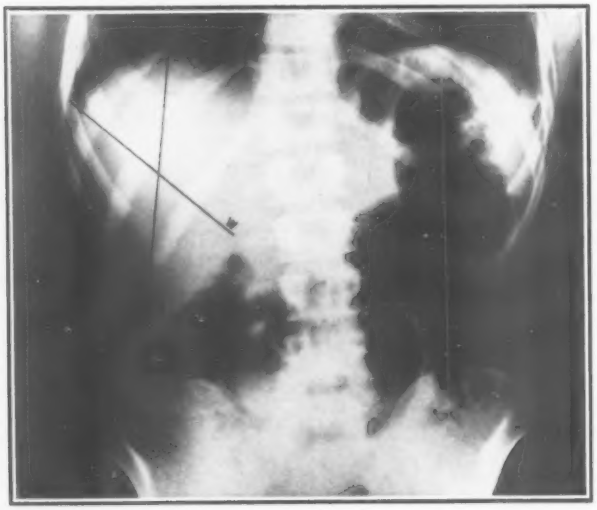

Fig. 1.—The gas contrast Roentgen visualization of liver and spleen, postero-anterior view, erect position, 40 inch tube-film distance. Measurements of the liver used in this study are indicated.

Fig. 2.—The gas contrast Roentgen visualization of liver and spleen, left anterior oblique view, erect position, 40 inch tube-film distance. Measurements of the spleen used in this study are indicated.

eter being the greatest diameter perpendicular to the long diameter. All heart measurements were taken from roentgenograms of the chest made at 6-foot tube-film distance, in the erect position, with respiration suspended in inspiration, and exposures of 1/10 second. The chest roentgenograms used in this study were unselected, in the sense that the films of the most recently necropsied patients were examined serially until the required number of patients with the proper time intervals between Roentgen and necropsy examinations were found. Eliminated from consideration, however, were those chest roentgenograms proved unsuitable for measurement, because of poor Roentgen technique, loss of the right heart border in the shadow of the spine, abnormalities of thoracic structure, or pulmonary pathology distorting the heart. Also excluded were those whose roentgenograms indicated the presence of emphysema, pericardial fluid, or congestive heart failure indicated by pulmonary or hilar congestion, since changed Roentgen measurements of such hearts would not be expected to parallel changes in heart weight.

After all measurements were obtained and recorded, the necropsy protocols were examined, and weights of organs obtained for correlations (Tables 1, 2, 3).

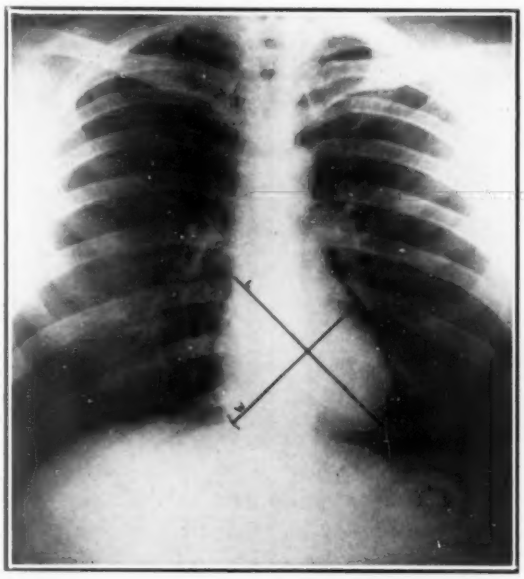

Fig. 3.—Roentgenogram of chest, postero-anterior view, erect position, 6-foot tube-film distance. Measurements of the heart used in this study are indicated.

The product of the two Roentgen diameters LxW was used in the case of each organ for correlation with necropsy weights (Figs. 4, 5, 6). Employing the Pearson product moment method embodied in the formula (Croxton[3])

$$r = \frac{N\Sigma XY - \Sigma X \Sigma Y}{\sqrt{[N\Sigma X^2 - (\Sigma X)^2][N\Sigma Y^2 - (\Sigma Y)^2]}}$$

the following coefficients of correlation were obtained:

TABLE 1.—ROENTGEN MEASUREMENTS AND WEIGHTS AT NECROPSY OF 19 LIVERS, ARRANGED IN ORDER OF INCREASING WEIGHT, WITH INTERIM BETWEEN ROENTGEN EXAMINATION AND DEATH INDICATED IN EACH CASE

LIVERS

| Roentgen | | | Autopsy | Interim |
|---|---|---|---|---|
| L cm. | W cm. | LxW $cm.^2$ | Weight gm. | Mos.Days |
| 15 | 14 | 210 | 1230 | 0-29 |
| 19 | 16 | 304 | 1380 | 0-28 |
| 25 | 17 | 425 | 1400 | 0-26 |
| 20 | 15 | 300 | 1410 | 1-7 |
| 23 | 16 | 368 | 1830 | 0-17 |
| 21 | 13 | 273 | 1900 | 1-24 |
| 23 | 18 | 414 | 2080 | 0-23 |
| 22 | 16 | 352 | 2180 | 0-19 |
| 20 | 15 | 300 | 2300 | 1-16 |
| 26 | 24 | 624 | 2370 | 2-4 |
| 24 | 15 | 360 | 2400 | 2-12 |
| 20 | 16 | 320 | 2530 | 1-10 |
| 27 | 16 | 432 | 2800 | 2-12 |
| 30 | 18 | 540 | 3140 | 0-14 |
| 23 | 13 | 299 | 3200 | 0-30 |
| 25 | 16 | 400 | 3350 | 2-8 |
| 25 | 16 | 400 | 3800 | 1-17 |
| 24 | 14 | 336 | 6000 | 2-3 |
| 33 | 21 | 693 | 6500 | 2-24 |

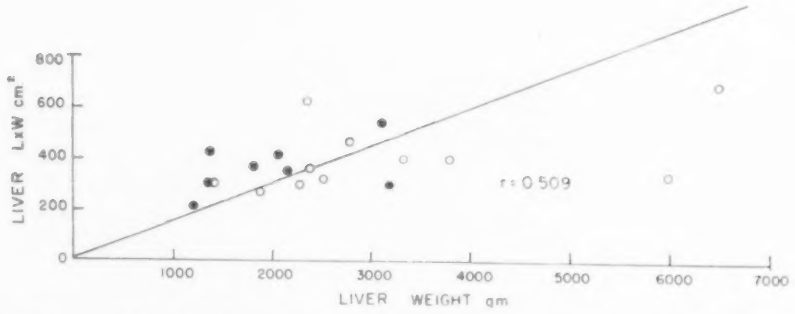


Fig. 4.—Liver weights plotted against products of the two measured Roentgen diameters. The dark circles represent those cases Roentgen-rayed in the last month of life, the light circles those Roentgen-rayed more than 1 but less than 3 months before death. The line was drawn by eye.

for 19 livers, interim less than 3 months, 0.509
for 8 livers, interim less than 1 month, 0.450
for 20 spleens, interim less than 3 months, 0.718

These correlations differ significantly from zero at the 5% level for liver, and at the 1% level for heart and spleen. The differences among the correlations, however, are not significant for this number of cases. Thus, the difference

TABLE 2.—ROENTGEN MEASUREMENTS AND WEIGHTS AT NECROPSY OF 20 SPLEENS, ARRANGED IN ORDER OF INCREASING WEIGHT, WITH INTERIM BETWEEN ROENTGEN EXAMINATION AND DEATH INDICATED IN EACH CASE

SPLEENS

| Roentgen | | | Autopsy | Interim |
|---|---|---|---|---|
| L cm | W cm | LxW $cm^2$ | Weight gm | Mos. Days |
| 7 | 3 | 21 | 95 | 0-30 |
| 11 | 4 | 44 | 100 | 0-23 |
| 11 | 7 | 77 | 100 | 0-29 |
| 10 | 5 | 50 | 120 | 1-10 |
| 9 | 3 | 27 | 130 | 2-24 |
| 7 | 5 | 35 | 150 | 2- 3 |
| 8 | 3 | 24 | 170 | 1-24 |
| 11 | 5 | 55 | 180 | 2- 8 |
| 12 | 8 | 96 | 240 | 0-28 |
| 11 | 6 | 66 | 280 | 0-19 |
| 10 | 4 | 40 | 295 | 0-17 |
| 8 | 3 | 24 | 300 | 1-17 |
| 13 | 6 | 78 | 300 | 1-16 |
| 12 | 6 | 72 | 340 | 0-26 |
| 15 | 7 | 105 | 355 | 2- 4 |
| 14 | 6 | 84 | 370 | 2-12 |
| 12 | 4 | 48 | 400 | 2-12 |
| 18 | 10 | 180 | 445 | 1- 7 |
| 18 | 8 | 144 | 550 | 0-12 |
| 19 | 10 | 190 | 1880 | 0-14 |

for 9 spleens, interim less than 1 month, 0.848
for 20 hearts, interim less than 3 months, 0.623
for 9 hearts, interim less than 1 month, 0.622

between the correlation coefficients for liver and spleen would require 62 cases to achieve significance at the 5% level.

**Discussion.** The product LxW is taken to represent a relative index of the Roentgen area. The fact that the

TABLE 3.—ROENTGEN MEASUREMENTS AND WEIGHTS AT NECROPSY OF 20 HEARTS, ARRANGED IN ORDER OF INCREASING WEIGHT, WITH INTERIM BETWEEN ROENTGEN EXAMINATION AND DEATH INDICATED IN EACH CASE

HEARTS

| Roentgen | | | Autopsy | Interim |
|---|---|---|---|---|
| L cm. | W cm. | LxW $cm.^2$ | Weight gm. | Mos.Days |
| 13 | 11 | 143 | 195 | 2-22 |
| 13 | 9 | 117 | 260 | 0- 9 |
| 14 | 11 | 154 | 290 | 1- 2 |
| 13 | 10 | 130 | 295 | 0-12 |
| 15 | 12 | 180 | 310 | 2- 8 |
| 14 | 11 | 154 | 330 | 1-29 |
| 13 | 11 | 143 | 350 | 0-21 |
| 16 | 11 | 176 | 360 | 1- 5 |
| 14 | 11 | 154 | 365 | 0-20 |
| 15 | 12 | 180 | 370 | 1-10 |
| 16 | 13 | 208 | 370 | 1-20 |
| 13 | 11 | 143 | 385 | 0- 8 |
| 15 | 12 | 180 | 400 | 2-22 |
| 21 | 13 | 273 | 430 | 0-15 |
| 16 | 11 | 176 | 450 | 2-22 |
| 18 | 13 | 234 | 510 | 1-26 |
| 15 | 13 | 195 | 550 | 2- 2 |
| 18 | 14 | 252 | 600 | 0-27 |
| 15 | 11 | 165 | 655 | 0-11 |
| 17 | 13 | 221 | 655 | 0- 6 |

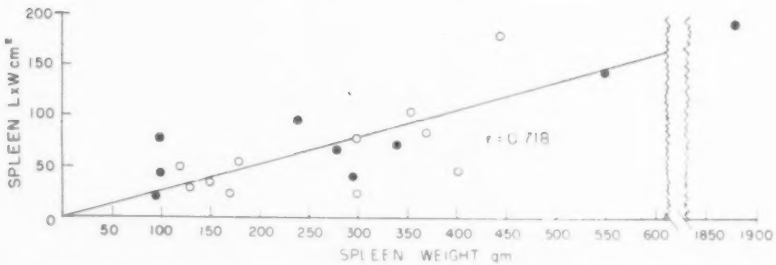


Fig. 5.—Spleen weights plotted against products of the two measured Roentgen diameters. The dark circles represent those cases Roentgen-rayed in the last month of life, the light circles those Roentgen-rayed more than 1 but less than 3 months before death. The line was drawn by eye.

Roentgen silhouette of the liver is a triangle, the spleen a semioval, and the heart an oval does not invalidate the use of LxW in each case for the purpose of correlation, since the use of the appropriate arithmetical constant (area of right-angled triangle = ½ LxW; area of semioval = $\pi/8$ LxW; area of oval = $\pi/4$ LxW) would have no effect in changing the correlation coefficients.

The coefficients of correlation obtained between the product of the to the measurement of a significant pair of such diameters. The substitution of necropsy weight for size further reduces expected correlation, but was used here because necropsy measurements of size were not consistently available. The time interval between Roentgen and necropsy examinations allows further loss of correlation, since changes in organ size certainly occurred in many of the patients, whose causes of death included metastatic carcinoma, leukemia, and lymphoma.

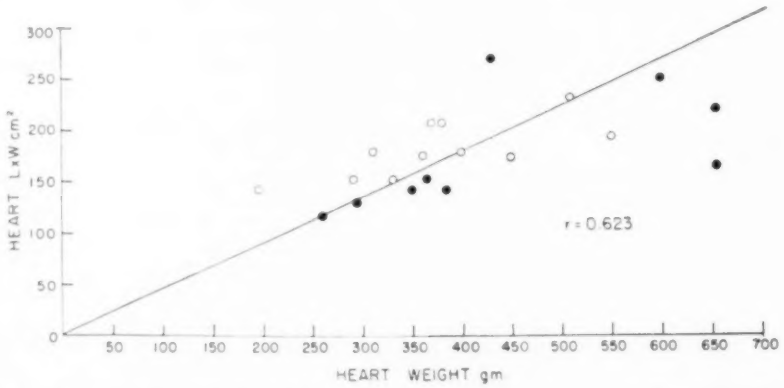


Fig. 6.—Heart weights plotted against products of the two measured Roentgen diameters. The dark circles represent those cases Roentgen-rayed in the last month of life, the light circles those Roentgen-rayed more than 1 but less than 3 months before death. The line was drawn by eye.

Roentgen diameters LxW and necropsy weights of the organs are not in themselves sufficiently great to inspire confidence in the reliability of the Roentgen representations of the organs concerned. There are a number of reasons for this low level of correlation. The index of Roentgen area used, LxW, takes no account of the third dimension of the organ nor of its irregularity of contour. In the case of the liver, the 2 diameters chosen were not at right angles to one another, as was the case with the other 2 organs, because of the fact that the Roentgen shadow of the liver did not lend itself readily

To evaluate the significance of these relatively low correlations between liver and spleen weights at necropsy and indices of their Roentgen areas, a similar correlation was obtained between the weight at necropsy of the heart and a comparable index of its Roentgen area. The heart provides an excellent control for this purpose, in that it is ordinarily well visualized by air contrast in routinely obtained roentgenograms of the chest, and its Roentgen measurements have been well studied and related to actual heart size (Ungerleider and Gubner[6]). The fact that the heart is a hollow organ

while the liver and spleen are spongy organs introduces still another variable, though one which appears less significant when it is considered that the contained blood volumes of the 3 organs are fairly comparable relative to their size. Thus, the capacity of the normal heart is approximately 400 ml. (Best and Taylor[1]), the blood content of the normal liver has been estimated at 1500 ml. (Ludwig[4]), and the spleen is capable of contracting to half its volume (Best and Taylor[2]). For the purpose of this study, it suffices that Roentgen visualizations of liver and spleen are comparable in reliability with that of the heart, the Roentgen representation of which has long enjoyed clinical confidence.

**Summary.** Roentgen visualization of the liver and spleen is obtained by gas contrast, in the erect position, after inflation of the stomach by Seidlitz powder and the colon by air insufflation. Twenty patients so examined died and were necropsied within 3 months of the examination. Statistical correlations were obtained between Roentgen measurements of the liver and spleen and their weights at necropsy. Though subject to the play of a number of variables, which are discussed, tending to lower correlation, the coefficients obtained proved comparable to that between Roentgen measurements of the heart and its weight at necropsy. It is concluded that Roentgen representations of the liver and spleen obtained with the gas contrast method warrant the degree of clinical confidence accorded the Roentgen representation of the heart.

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## SUMMARIO IN INTERLINGUA

### Evalutation Necroptic Del Roentgeno-Visualisation De Hepate E Splen, Con Gas Como Medio De Contrasto

Roentgeno-visualisation de hepate e splen es obtenite per contrasto a gas, in position erecte, post inflation del stomacho per pulvere de Seidlitz e del colon per le insufflation de aere. Vinti patientes subjicite a iste examine moriva e esseva necropsiate intra 3 menses postea. Correlationes statistic esseva obtenite inter le mesurationes roentgenologic de hepate e splen e le pesos de iste organos al necropsia. Ben que afficite per plure variabiles que tendeva a reducer le correlation (e que es discutite), le coefficientes obtenite esseva comparabile a illos existente inter le mesurationes roentgenologic del corde e su peso al necropsia. Es concludite que representationes roentgenologic de hepate e splen, quando obtenite per medio del methodo a contrasto per gas, merita le mesme grado de confidentia clinic como representationes roentgenologic del corde.

# THE PROBLEM OF LEVARTERENOL (LEVOPHED) EXTRAVASATION AN EXPERIMENTAL STUDY

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Levarterenol (Levophed) is a valuable drug for the treatment of various types of shock due to surgery, trauma, drug reaction or myocardial infarction (Kask[10], Salomon[19], Sampson and Griffith[20]). It is also an effective adjuvant in the therapy of acute renal failure secondary to vasomotor collapse (Mattingly[12]). One of the drawbacks to the use of this life-saving drug has been the occurrence of ischemia and subsequent necrosis in an area in which the drug has infiltrated (Bergmann[3], Greenwald *et al.*[6], Kurland and Malach[11], Shapiro and Perlow[21], Uricchio, Calenda and Cutts[22]). Strangely, this sequence of events can occur even in the absence of infiltration with the needle perfectly in place and the infusion running well. It has previously been established that both phentolamine (Regitine), McGinn, Schluger and DiGregorio[15], Zucker[23]) and piperoxan (Benodaine) (Pelner[16]) can reverse the ischemia if infiltrated by multiple punctures into the ischemic area. This report is based on an experimental study to compare the actions of these two substances and to determine any possible superiority of one or the other. We also attempted to determine if the addition of certain substances to the levarterenol infusion could prevent the ischemia and necrosis resulting from infiltration.

It has become apparent that unless something is done to make the levarterenol infusion safe, this remarkable drug may fall into disrepute. Considering the fact that many lives can be saved by its appropriate use, this would be a definite therapeutic loss. A very active cardiologist told one of the authors that he would not use a levarterenol infusion, no matter what the occasion, because of the fear of a lawsuit if infiltration occurred with consequent ischemia and necrosis. Under the circumstances, the fact that the ischemia can be reversed rather simply should be widely publicized. It would be even better if another substance could be added to the levarterenol infusion which could reverse the effect of the infiltration, if it occurred.

Shapiro and Perlow[21] reported 6 cases of skin necrosis after intravenous administration of levarterenol. They state that the number of instances of severe local ischemia and transient phlebitis not associated with skin necrosis is not known, but is undoubtedly much more frequent than actual necrosis. They believe that local infiltration and stagnation of the drug in the vein may be the important factors

in producing skin necrosis. In the case of stagnation, diffusion of the solution through the wall of the vein would offer an explanation for involvement of the tissue along its course.

de Alvarez and his co-workers[1] noted that levarterenol, when infused intravenously, sometimes produces marked generalized vasoconstriction with ischemic necrosis at points remote from the site of infusion. In one of their patients, a necrotic area developed on the hand, and, in another, in the conjunctiva. Such remote ischemia is unusual, however, in the opinion of most observers as judged from a perusal of current literature. There are many other instances in the literature of the occurrence of ischemia and necrosis following levarterenol extravasation.

TREATMENT OF LEVARTERENOL EXTRAVASATION. Until recently the methods of treatment used for ischemic areas after levarterenol infiltration or extravasation have proved largely unsuccessful. Injections of hyaluronidase and procaine (Hardie and Hunter[7]) into the ischemic area have not prevented necrosis, nor has nourishment of the vein wall by transfusions of oxygenated whole blood changed the picture (Hardie and Hunter[7]). Some authors recommend the use of a cannula or polyethylene tube instead of a needle for the infusion. That this is not the answer is suggested by Humphreys, Johnston and Richardson[9], who have reported 2 cases of skin necrosis in patients thus treated.

Fortunately several articles have appeared recently describing a treatment that has proved successful.

McGinn, Schluger and DiGregorio[15] used infiltration of phentolamine (Regitine) hydrochloride and hyaluronidase and Zucker[23] used phentolamine injected alone into the ischemic area, a pinking out of the area occurring in from 5 to 10 minutes. Phentolamine is a physiological antagonist to levarterenol and is used in the diagnosis of pheochromocytoma, a tumor of the adrenal medulla, which produces levarterenol. The technique of the treatment involved the use of 5 mg. of phentolamine in 20 ml. of water, in one instance with, and in the other without, the addition of a solution of hyaluronidase. We would be hesitant to use hyaluronidase ourselves, since it will cause a diffusion not only of phentolamine but of the levarterenol as well. In any event, multiple infiltrations of a solution of phentolamine alone work just as well.

Another effective method of treatment, using a different antagonist of levarterenol, was previously described by one of the authors (Pelner[16]). A solution of piperoxan (Benodaine), 5 mg. in 2.5 ml. or ¼ of an ampul, was added to 17.5 ml. of sterile saline solution. About 0.25 to 0.5 ml. of this solution was injected subcutaneously into the ischemic, cold area, first into sites around the periphery and then at points about 1 cm. apart within the area. Within 30 to 50 seconds, each injected area developed a pink coloration and became warm to the touch. A total of more than 20 ml. is often used. Thirty milliliters was used in one patient in whom a very satisfactory result was obtained. In one instance, a higher concentration of piperoxan was used (10 mg. in 5 ml.) and was added to 15 ml. of sterile saline solution for infiltration because of the large amount of levarterenol used in the infusion.

SOME PERTINENT PREVIOUS EXPERIMENTAL STUDIES. There is a definite species difference with regard to the effect of levarterenol infiltration. A small extravasation, probably not more than 10 ml. of diluted levarterenol solution, can produce ischemia and necrosis in humans. There must be an

individual susceptibility factor in humans since every infiltration does not necessarily result in necrosis, regardless of size. deAlvarez *et al.*[1] found that they could not produce ulceration in dogs by intracutaneous injection of levarterenol. Subcutaneous administration, however, did produce such ulceration in 2 animals when injected so as to produce tension. Under conditions of shock these authors could not produce tissue ulceration in dogs following intravenous administration of levarterenol. With patients in shock, extravasation can occur, even though the needle is properly set in the vein and has not been dislodged. In dogs, de Alvarez *et al.*[1] found that necrosis occurred only at the site where extravasation was permitted.

Berben, Bryant and Howard[2] likewise, tried to produce extravasation in dogs. They found that the *rapid* injection of 100 ml. of levarterenol solution into the subcutaneous tissues did not produce soft tissue necrosis; however, the *slow* infusion of the same quantity of test solution into the subcutaneous tissues over a 50- to 70-minute period routinely resulted in necrosis. Berben, Bryant and Howard found that although the intravenous administration of levarterenol into medium-sized veins resulted in marked venous spasm, it did not produce skin necrosis in the absence of extravasation. This rules out the possibility, in dogs at least, that prolonged spasm of the veins in the region of the intravenous infusion might cause tissue necrosis.

McGinn and Schluger[14] attempted to demonstrate in rabbits the value of phentolamine as a treatment for levarterenol infiltration. They found that they could not produce skin necrosis by a single subcutaneous levarterenol injection. They found that a *continuous subcutaneous* injection would produce necrosis, but the period of administration had to be prolonged for more than an hour. From this observation, they drew the conclusion that the extent of damage from a levarterenol injection seems to be a function of the time of exposure rather than of the total amount of levarterenol introduced or its concentration. They found that infiltration of phentolamine was successful in reversing the ischemia produced by *slow* levarterenol infiltration.

Zucker[23] noted that the *intracutaneous* injection of 1 ml. of levarterenol solution (1 mg. per ml.) on the shaved abdomen of a rabbit regularly resulted in an area of ischemic necrosis. Note that this concentration is about 250 times the concentration usually used clinically. However, apparently because of species difference, a stronger solution must be used in the rabbit regularly to produce ischemia and necrosis. An intracutaneous injection of the strength noted produced a wheal with a blanched center, which resulted in an area of necrosis 24 hours later.

To counteract the ischemia, Zucker injected 1 ml. of a solution of phentolamine (Regitine), 1 mg. per ml. He found that if this solution is infiltrated in the ischemic area within 6 hours, the ischemia was reversed and necrosis did not develop. However, if 24 hours elapsed before the antagonist was given, necrosis usually developed.

EXPERIMENTAL STUDIES AND RESULTS. The following experiments were performed to determine the efficiency of several agents in the prevention of necrosis after Levophed. Each of 6 adult rabbits of about the same size and age was injected intracutaneously on the shaved abdomen at three sites with 1 ml. of Levophed (1 mg. per ml.). An ischemic wheal of 20 to 30 mm. was invariably produced. It is known from Zucker's work[23] that this amount and concentration of Levophed regularly

Fig. 1.—Scheme of the experiment.

produces ischemia and subsequent necrosis. In each rabbit one wheal was allowed to act as a control site except in rabbit No. 3 (see below). The other wheals were secondarily injected with Regitine, or Novocain, or Benodaine in the amounts and at the time intervals shown in Fig. 1. The concentrations used were respectively Regitine (1 mg. per ml.) Benodaine (2 mg. per ml.) and Novocain 1 or 2% as indicated in Fig. 1. The secondary infiltration was carried out in multiple areas.

In each instance Levophed alone invariably produced ischemia and subsequent necrosis at the control site. In each instance Regitine and Benodaine prevented necrosis provided that the medicament was injected not later than 18 hours after the Levophed injection. When given 24 hours later, necrosis occurred (Rabbit No. 6). Novocain in no instance prevented necrosis.

In Rabbit No. 3 the Levophed at the first test site was mixed with Meticortelone, 1 ml. (25 mg. per ml.), at the second site with Solu-Cortef, 1 ml. (50 mg. per ml.), and at the third site with heparin, 1 ml. (10 mg. per ml.). This was to determine if the combination of some other medicament with the Levophed would prevent ischemia and necrosis. The adrenal steroids are known to diminish capillary

Fig. 2.—Levarterenol infiltration. Photomicrograph shows loss and necrosis of the squamous cells, destruction of hair follicles, swelling, separation and loss of staining characteristics of the hyaline fibers (magnif. 154 ×).

permeability. Nevertheless in sites 1 and 2 ischemia and necrosis did occur and if anything more rapidly in spite of the steroids. Heparin, however, did prevent necrosis.

This entire experiment was repeated three times. The same rabbits were used after an interval of 4 weeks during which the denuded skin had healed after each experiment. In one additional experiment, solutions of Levophed, Meticortelone and heparin were mixed (1 ml. of each in the concentration above mentioned) and injected intracutaneously. There was no resultant necrosis. Histologic studies of the injected areas showed that the intracutaneous injection of 1 ml. of Levophed (1 mg. per ml.) invariably caused necrosis unless reversed by the antagonists. When no antagonist was used there occurred necrosis and eventual loss of squamous cells, obstruction of the hair follicles, swelling, separation and loss of staining characteristics of the hyaline fibers and necrotic foci in the depths of the area (Figs. 2 to 8).

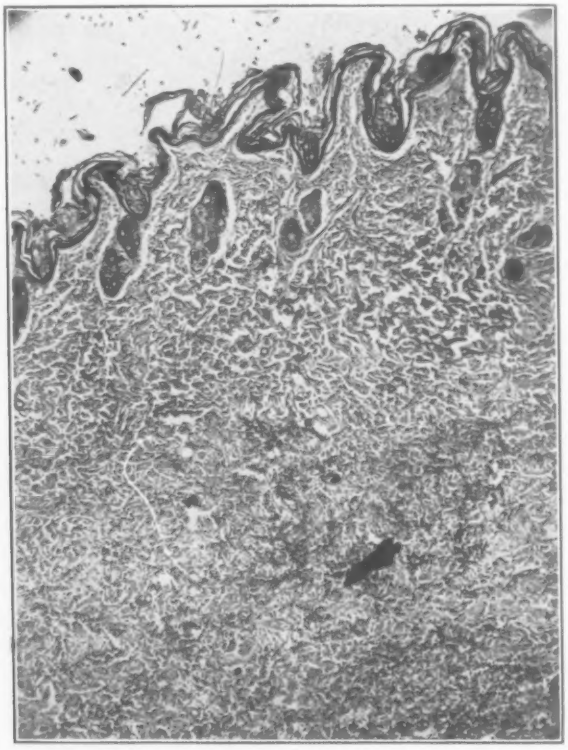

Fig. 3.—Levarterenol infiltration. Phentolamine reversal 2 hours after. Photomicrograph shows less damage to squamous cells and hyaline fibers (magnif. 154 ×).

Novocain was without effect histologically in preventing necrosis.

**Discussion and Comment.** As shown by the experimental study, both phentolamine (Regitine) and piperoxan (Benodaine) resulted in a satisfactory reversal of the ischemic wheal pro-

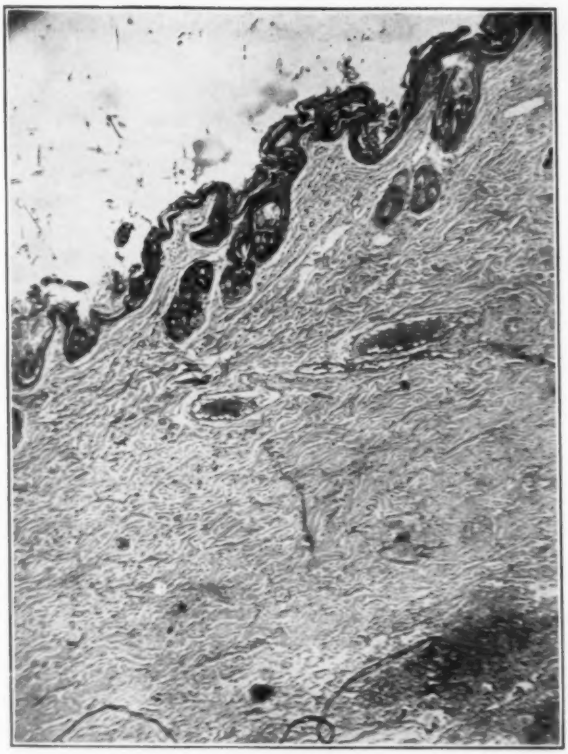

Fig. 4.—Levarterenol infiltration. Piperoxan reversal 2 hours after. Photomicrograph shows very little damage to squamous cells or hair follicles and hyaline fibers (magnif. 154 ×).

Fig. 5.—Levarterenol infiltration. Treatment with 2% procaine. Loss of upper layer of squamous cells. Hyaline fibers poorly stained. Large area of necrosis in center of field (magnif. 154 ×).

duced by levarterenol (Levophed). These salutary effects occurred when either of these substances was infiltrated in the affected area up to and including 18 hours after the initial levarterenol injection. After 24 hours had elapsed, neither of these substances was effective in reversing the ischemia. Therefore, to prevent necrosis, the involved area must be infiltrated with either phentolamine or piperoxan before 18 hours have elapsed. There was little difference grossly in the effectiveness of these two substances. Microscopically, however, piperoxan appeared slightly more effective, since the subsequent biopsy findings were more nearly normal.

It would, indeed, be useful if another substance could be given in combination with the levarterenol solution to prevent the ill effects of infiltration should this occur. We had hoped that the corticosteroids might prove beneficial in this manner.

One of the derangements of the peripheral vascular tree in shock is an increase of capillary permeability. Rhoads, Wolff and Lee[18], studying the traumatic shock of burns, noted that when large plasma transfusions were administered to a burned patient, there was not as great a rise in plasma volume as had been anticipated, and that even this rise was only temporary. This was evidence of continued extra-

Fig. 6.—Levarterenol and prednisolone infiltration. Loss of upper layers of squamous cells and hair follicles. Area of necrosis in lower border of field (magnif. 154 ×).

vasation of protein. The author estimated that a period of 40 hours was required for the recovery of the capillary walls to their normal state of permeability. When the patients were given adrenal cortical extract the loss of transfused plasma was decidedly less, and the plasma volume returned to normal considerably earlier.

It is released from infected or damaged tissue, causing local vasodilatation, increase in capillary permeability and migration of leukocytes.) Freed and Lindner[4] confirmed the work of Menkin, and also found that adrenal cortical extract prevented the action of leukotaxine in increasing capillary permeability.

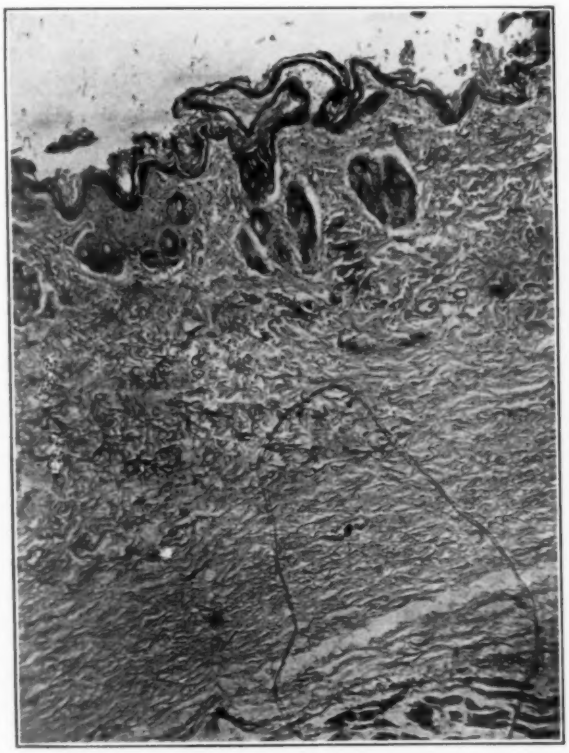

Fig. 7.—Levarterenol and heparin infiltration. Photomicrograph shows better preservation of hyaline fibers and squamous cells (magnif. 154 ×).

Menkin[13] noted that nitrogenous products liberated by tissue injury such as leukotaxine markedly increase capillary permeability, and that this effect is held in abeyance by an extract of adrenal cortex. (Leukotaxine is a crystalline nitrogenous substance isolated from inflammatory exudates and is not related to histamine or acetylcholine.

Hayashi, Funaki and Ono[8] found that the administration of cortisone strikingly inhibited the accumulation of trypan blue from the circulating blood into a skin area injected with leukotaxine.

For these several reasons, it was hoped that if a corticosteroid were added to the levarterenol infusion, the

capillary permeability present in shock might be reversed and levarterenol leakage would be less likely to occur. It was also postulated that in view of the well-known antiinflammatory action of the cortical extracts, perhaps this action might antagonize the ill effect of the ischemia if the infiltration occurred. However, this did not prove to be true. Necrosis occurred in our experiments in spite of the combined injection of Solu-Cortef (hydrocortisone) or Meticortelone (prednisolone) with levarterenol. The necrosis was even more marked than usual. However, our experiment did show that the additive necrotic effect of the corticosteroid could be mitigated by the inclusion of heparin (q.v.) in the mixture.

Sampson and Griffith[20] made the significant observation that levarterenol when used alone, often results in thrombosis and necrosis of the vein employed, at or near the site of injection, especially if the drug escapes into the surrounding tissues. However, they also found that if 10 mg. of heparin is added to each 500 ml. of 5% glucose solution containing 8, 12 or even 16 mg. of levarterenol, this would prevent thrombosis or necrosis of the veins. They noted that, even if a small amount of the solution should escape into the tissue, the resulting inflamma-

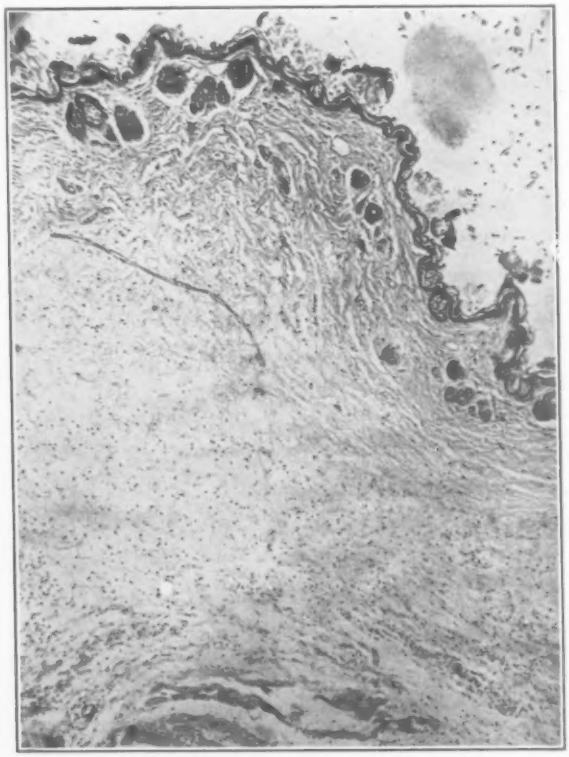

Fig. 8.—Levarterenol and prednisolone and heparin infiltration. Heparin has a somewhat salutary effect on necrosis, but does not entirely prevent it as viewed microscopically. No necrosis was found on gross examination.

tory reaction did not progress to necrosis.

If these clinical findings can be duplicated, the problem of administration of levarterenol is indeed solved. Our experimental results using heparin and levarterenol solution together seem to bear out Sampson and Griffith's contention, except that we found no evidence of vascular thrombosis on microscopic study. Regardless of the nature of action of heparin, however, it would seem prudent henceforth to add 10 mg. of heparin to the levarterenol solution. In patients with cardiogenic shock, this would not be contraindicated, and might even be useful. However, in postoperative shock, even this small mount of heparin might increase the probability of bleeding, and, therefore, should not be used. Since in our experiments the mixture of levarterenol, Meticortelone and heparin caused decidedly less necrosis than levarterenol with Meticortelone, this mixture might warrant consideration for patients in severe shock. The use of a corticosteroid combined with levarterenol in patients with severe shock has an excellent experimental background (Fritz and Levine[5], Ramey, Goldstein and Levine[17]), and has been used successfully in practice.

**Summary and Conclusions.** 1) The problem of levarterenol (Levophed) extravasation and resultant necrosis is a serious one. 2) The value of the physiological antagonists phentolamine (Regitine) and piperoxan (Benodaine) in preventing necrosis has been demonstrated experimentally in rabbits. 3) Procaine in 1% or 2% solution is without effect in preventing ischemia or necrosis in rabbits. 4) Consideration should be given to including 10 mg. of heparin in each levarterenol infusion in humans, since in animal experiments this combination prevented necrosis. 5) Heparin should probably also be added to the currently used levarterenol and hydrocortisone, or levarterenol and prednisolone infusions. 6) Further study is indicated to determine if the results of these experiments can be applied to humans.

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## SUMMARIO IN INTERLINGUA

### Le Problema Del Extravasation De Levarterenol (Levophed) Un Studio Experimental

(1) Le problema del extravasation de levarterenol (Levophed) e del resultante necrosis es un problema seriose. (2) Le valor del antagonistas physiologic phentolamina (Regitina) e piperoxano (Benodaina) in prevenir le necrosis esseva demonstrate experimentalmente in conilios. (3) Procaina in solutiones de 1 o 2% es sin effecto in prevenir ischemia o necrosis in conilios. (4) Debe esser prendite in consideration le inclusion de 10 mg de heparina in omne infusion de levarterenol in humanos, proque in experimentos animal iste combination preveniva le disveloppamento de necrosis. (5) Il es probabile que heparina deberea etiam esser addite al currentemente usate infusiones de levarterenol e hydrocortisona o de levarterenol e prednisolona. (6) Studios additional es indicate pro determinar si le resultatos del presente experimentos pote esser applicate a humanos.

# THE MECHANISM OF EXPERIMENTAL GLOMERULONEPHRITIS PRODUCED IN RABBITS BY AVIAN ANTIKIDNEY SERA*

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When the production of experimental glomerulonephritis in rabbits by means of antirabbitkidney duck serum (ARbKDS) was introduced by Masugi[16] he did not mention that this disease seems to differ basically from the disease used previously by him and others (Lindemann[15], Masugi[16], Smadel[21]) in which a mammal was the recipient of an antiserum produced in another mammalian species against the recipient's kidneys. Throughout the literature, however, it is apparent that wherever the latter type of disease was produced, signs of the disease appear immediately after the injection of the immune serum, provided that sufficient amounts of such a truly nephrotoxic serum are injected (Table 1). Masugi noticed, however, that at least 5 days elapsed after the injection of duck immune sera before signs of disease appeared. Similarly all other observers using avian sera for the production of immune nephritis have noticed a considerable time interval between the time of injection and the morphologic or functional appearance of disease. Only Hasson, Bevans and Seegal[5] have recently described that they were able to produce "immediate" experimental glomerulonephritis in rats with the use of antiratkidney duck sera. If one analyzes their data, however, one will find that they gave occasionally 2 but mostly 3 injections of immune serum at 24-hour intervals and started to count the interval between injection and appearance of disease only from the last injection. With the most potent sera they described that increased proteinuria was noticed 24 hours after the *last* injection, that is, on the 4th day after the first injection, which actually sets off the immune process; this demonstrates again a considerable interval in contrast to the immediate disease induced by mammalian sera in rats and rabbits and dogs. Kay[8] has stressed this difference and offered an hypothesis for the mechanism of the disease induced by avian sera which clearly

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differentiates it from the disease induced by mammalian sera. Kay suggested that the antirabbitkidney duck serum (ARbKDS) has actually 2 components: one *localizing* fraction which immediately upon injection forms an antigen-antibody union with the glomerular apparatus but is unable to produce disease due to the class difference between the injected antibody and the recipient animal; the second, normal duck serum protein itself, serves to stimulate antibody formation to duck serum by the antibody forming centers of the rabbit. When these antiduck-serum antibodies appear in the circulation after 4 or more days, they unite with the duck serum localized in the kidney and alter or destroy the glomerular cells which were coated with the localizing duck serum in an antigen-antibody reaction in which the antibody is now mammalian. We have suggested[11] that the initial failure to destroy or alter the glomerular structure is based on the inability of a union between mammalian antigen and avian antibody to use mammalian complement (Izumi[6]), an indispensable prerequisite for cell destruction in most instances. This idea was concurred in by Pressman, Korngold and Heymann[19] who showed with the radioactive iodine labeling technique that indeed the localizing fraction of the duck serum immediately upon injection unites with the glomerular structures without producing disease. We showed that the union is not accompanied by a fall in complement (C′) while there is ample evidence (Lange[12], Stavitsky, Hackel and Heymann[22]) of fall in C′ in the case of the rat disease induced by rabbit immune sera. Kay was able to prevent the delayed disease from occurring when he gave full body Roentgen-ray irradiation to the rabbits prior to the injection of the ARbKDS thus preventing antibody formation[8]. This suppression of antibody formation was documented by the failure of antiduck-serum antibodies (precipitins) to appear in the blood of such animals and by the slow disappearance rate of duck serum from the recipient's blood. Zoellinger[25] and we[13] also showed that

TABLE 1.—INFLUENCE OF THE SOURCE OF NEPHROTOXIC SERA AND OF THE SPECIES OF THE RECIPIENT ANIMALS ON THE DELAY PERIOD ELAPSING BETWEEN INJECTION AND APPEARANCE OF DISEASE

| *Author* | *Year of Publication* | *Donor Organ* | *Intermediary Antibody Producer* | *Recipient Animal* | *Period of Delay* |
|---|---|---|---|---|---|
| Lindeman, W. | 1900 | rabbit kidney | guinea pig | rabbit | none |
| Masugi, M. | 1933 | rat kidney | rabbit | rat | none |
| Smadel, W. | 1937 | rat kidney | rabbit | rat | none |
| Seegal, B. | 1946 | rat placenta | rabbit | rat | none |
| Heymann, W. | 1951 | rat kidney | rabbit | rat | none |
| Stabley, R.W. | 1956 | dog kidney | rabbit | dog | none |
| Stickler, G.B. | 1956 | dog kidney | rabbit | dog | none |
| Mellors, R.C. | 1956 | rabbit kidney | goat | rabbit | none |
| Masugi, M. | 1934 | rabbit kidney | duck | rabbit | more than 5 days |
| Fouts, P.I. | 1941 | dog kidney | chicken | dog | more than 5 days |
| Kay, C.F. | 1942 | rabbit kidney | duck | rabbit | more than 4 days |
| Lange, K. | 1951 | rabbit kidney | duck | rabbit | more than 4 days |
| Lange, K. | 1955 | rat kidney | duck | rat | more than 3 days |
| Stavitsky, A.B. | 1956 | rat kidney | duck | rat | more than 3 days immediate in 10%. |
| Lange, K. | 1957 | rabbit kidney | chicken | rabbit | more than 4 days |

cortisone used instead of total body Roentgen-ray irradiation suppressed or depressed formation of antibodies against duck serum and prevented or markedly ameliorated the disease. Kay[9] noticed, however, that the transfusion of blood of rabbits with high antibody titers against unmodified duckserum into rabbits which were sensitized 24 hours before with ARbKDS did not result in immediate disease although these recipient animals had now by virtue of the transfused blood, good antibody levels against duck serum. Kay attributed this fact to an insufficient localization of the ARbKDS on the glomerulus within 24 hours which is in contradiction to later findings of Pressman, Korngold and Heymann[19] and of our own findings with the fluorescent antibody labeling technique described below noticing practically immediate localization.

Our studies were aimed at explaining these apparent discrepancies and to elucidate the actual immune mechanism of this experimental disease, which functionally as well as morphologically simulates most closely the human disease.

**Methods.** 1) THE IMMUNE SERUM. Pekin ducks of approximately 5 lbs. body weight, male or female, were injected intraperitoneally every other day with 10 ml. of a 10% suspension of rabbit kidney homogenate. The homogenate was produced from rabbit kidneys perfused *in situ* from artery to vein with at least 500 ml. of saline until they were completely free of blood. The injections of the homogenate were given for 2 weeks, followed by one week of rest and then a second series of injections for 2 weeks. One week after the last injection the ducks were bled by heart puncture. The serum of at least 7 but mostly 10 to 20 ducks was pooled to secure uniformity of the serum. All immune sera were stored at −20° C. and inactivated for 30 minutes at +56° C. before use. More recently the globulin fraction of such sera was used, produced by the method of Eisen and Pressman[18]. Hens of the Leghorn strain were treated in an identical fashion when chicken immune sera (ARbKCS) were produced.

2) THE RECIPIENT ANIMALS. Male albino rabbits of the New Zealand strain weighing approximately 5 lbs. were used throughout. They were fed Purina rabbit pellets and water *ad lib.* The animals were weighed daily and the total daily urine output was examined for protein semiquantitatively with 20% sulfosalicylic acid or quantitatively with the biuret method (Kingsley[10]). Blood specimens were obtained as often as desired from the central ear artery according to the method of Cohen[2]. It should be emphasized that this method permits the taking of sterile blood specimens as often and as large as desired, is rapid and does not endanger the animal. It has enabled us to carry out many of the studies described. When serum transfusions were given they consisted of 50 ml. of nephritic rabbit serum which was given after 25 to 35 ml. of blood was withdrawn from the recipient animal to avoid circulatory embarrassment.

3) BIOCHEMICAL DETERMINATIONS. Blood urea nitrogen was determined according to the method of Karr[7], blood cholesterol according to the method of Carr and Drekter[1] and plasma protein determinations according to the method of Weichselbaum[24].

4) IMMUNOLOGIC PROCEDURES. Precipitin tests were carried out according to the method described by Kay[8] and complement determinations according to the method described by us previously[14].

5) FLUORESCEIN LABELING TECHNIQUE. The technique of Coons and Kaplan[3] for labeling antibodies with fluorescein isocyanate was used. Antisera against rabbit gamma globulin were produced by the intravenous injection of 80 mg. of rabbit gamma globulin into ducks 3 times a week for 2 weeks followed by a week of rest and another 2-week period of immunization. One week after the last injection, the ducks were exsanguinated by heart puncture. The globulin fraction of this serum was labeled with fluorescein isocyanate.

The globulin fraction of the serum of rabbits made nephritic by 2 injections of ARbKDS, 1 ml. per lb., on 2 consecutive days was labeled with fluorescein isocyanate. The serum was drawn from the nephritic rabbits at the height of the disease, that is, approximately on the third day after its onset.

In addition the globulin fraction of the serum of rabbits immunized with unmodified duck serum was labeled with fluorescein isocyanate. Two intravenous injections of 1 ml.

per lb. of body weight were given to these rabbits on consecutive days and their blood was drawn between the sixth and ninth day after the injections, when they had developed high precipitin titers against duck serum.

The kidneys of rabbits were removed immediately after sacrifice; suitable small pieces were rapidly frozen in isopentane cooled in liquid nitrogen. Sections were cut at 5 mμ thickness in a cryostat at a temperature of −20° C. either immediately after they were frozen or after they were kept at −20° C.

**Results.** When rabbits were injected with ARbKDS, 1 ml. per lb., for 2 successive days, proteinuria invariably occurred between the fourth and sixth day after the first injection. There was no marked variation in this delay of appearance of disease using different pools of ARbKDS. When the globulin fraction of an identical amount of serum was given, the disease appeared at the same time and was approximately of the same severity. When 3 injections of ARbKDS, 1 ml. per lb., were given on 3 successive days (9 rabbits), the delay period varied from 4 to 5 days and the severity of the disease was greater and more animals died earlier in the course of the disease in uremia. When 1.5 ml. per lb. were given on 2 or 3 successive days (5 rabbits), the delay period varied between 4 and 5 days and a very severe disease with rapid death in uremia resulted. When 15 ml. of ARbKDS were given to 8 rabbits in one injection, 4 of the animals died either immediately after the injection or within 10 hours thereafter. On necropsy they showed diffuse petechial hemorrhages on all mucous membranes, numerous petechiae in the kidney parenchyma and bloody urine in the bladder. The urine in those which survived became normal in 48 to 72 hours. On the fifth day, however, they developed severe proteinuria again with the typical clinical picture of glomerulonephritis developed by all animals given smaller doses of ARbKDS. In 254 animals given ARbKDS from different pools, we have never seen the appearance of acute glomerulonephritis before the fourth day. All animals sacrified before the fourth day and examined histologically and histochemically did not show any abnormalities (Wachstein and Lange[23]). Simultaneously with the appearance of the disease, antibodies against duckserum (precipitins) could be detected in all animals thus examined. The highest titer usually occurred on the second or third day of the disease and detectable titers against duckserum were still present 4 weeks after the onset in those animals which survived. When smaller amounts of ARbKDS were given the interval between the injection and onset of disease was prolonged. For each amount of ARbKDS injected a predictable delay of onset of disease could be established. We *never* succeeded, however, in shortening the interval to less than 4 days. In all these experiments the onset of disease was accompanied by a precipitous fall in serum complement.

Within 24 to 48 hours after the onset the blood urea nitrogen (BUN) begins to rise and rises to very high levels in those animals which show a prolonged and severe disease, often leading to death in uremia. Those animals receiving less than the standard dose of ARbKDS of 1 ml. per lb. on 2 successive days show a short lasting and milder elevation of BUN with a more rapid return of the urine to normal. The oliguria found in all animals for the first few days of overt disease is shorter and less pronounced in those receiving less than the standard dose of ARbKDS. Cholesterol values rise within one week in those animals with a sustained disease and often reach values of 4 times the normal. Total serum protein and serum albumin values become sub-

normal in the animals with a protracted proteinuria and an inversion of the A/G ratio occurs usually within 10 to 12 days.

If the antibody against normal duck serum were the disease-producing factor, it should be possible to replace part of the ARbKDS by unmodified duck serum (DS) as an antigen since, according to Kay, the localizing factor also carried out in 3 animals. As can be seen from Fig. 1, antiduckserum titers were found as usual on the fourth day but disease did not occur until the eighth and sixth day respectively. These delays were just as long as the delays observed when the small amounts of ARbKDS were given alone. Similarly the addition of human serum to 1.5 ml. of ARbKDS instead of DS (3 rabbits)

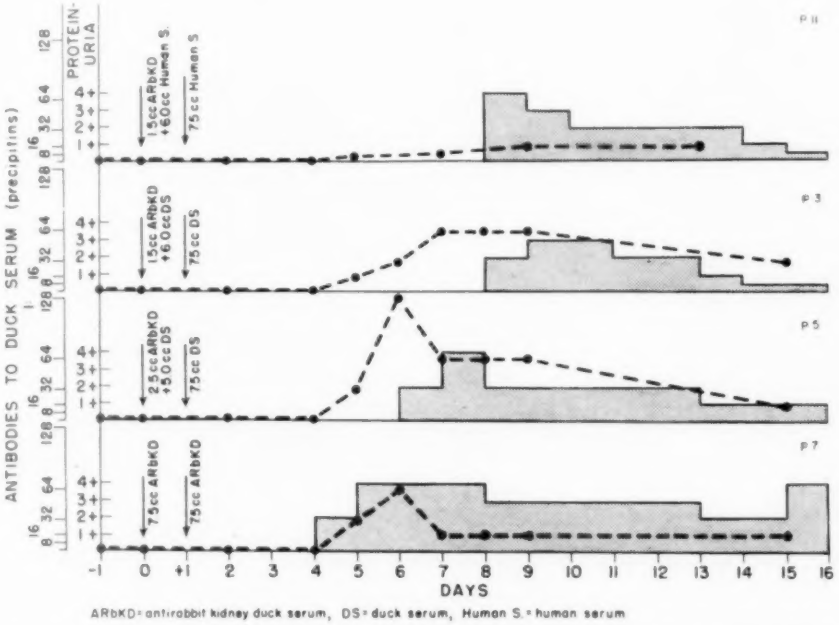


Fig. 1.—Influence of the amount of the injected antirabbitkidney duck serum and of the amount of unmodified duck serum or human serum on antiduck serum titers and appearance of proteinuria in rabbits.

acts only to prepare the site of the later union of the duck serum particle coat on the glomerulus and the antiduck serum antibody. We, therefore, replaced part of the ARbKDS by plain duck serum as shown in Fig. 1. The experiments using 1.5 ml. of ARbKDS and 13.5 ml. unmodified duck serum were carried out in 3 animals and the experiments using 2.5 ml. ARbKDS and 12.5 unmodified duck serum were reduced the antiduck serum titer noticeably but disease appeared with the same delay as if ARbKDS were given alone. It thus became apparent that antibodies against unmodified duck serum were not the decisive factor in the production of the disease.

The transfusion of 50 ml. of serum from rabbits with acute glomerulonephritis (produced by 2 injections of ARbKDS, 1 ml. per lb., and drawn

on the third day of the resultant disease, that is, 7 to 9 days after the first injection of ARbKDS) did not cause nephritis in 6 normal rabbits (Fig. 2). When 10 rabbits were sensitized with ARbKDS, 1 ml. per lb., however, and given a transfusion of 50 ml. of serum from rabbits with glomerulonephritis 24 hours later, proteinuria occurred within 24 hours in 7 and within 48 hours in the remaining 3. The latter group was anuric during the first 24 hours. Histologic examination of the kidneys of 2 of these animals sacrificed 6 hours after the serum transfusion showed the typical picture of acute glomerulonephritis (Fig. 3). When the globulin of ARbKDS was used for sensitization and only the gamma globulin of 50 ml. of nephritic rabbit serum was injected 24 hours later in 7 rabbits, disease also occurred without delay period (Fig. 4).

When identical amounts of either serum or gamma globulin of rabbits previously immunized against unmodified duck serum was transfused into 12 rabbits sensitized with ARbKDS the normally occurring delay period was not shortened. Similarly, sensitization with unmodified duck serum followed 24 hours later by transfusion of 50 ml. of nephritic rabbit serum did not induce glomerulonephritis in the recipient animal. Most of these experiments were also carried out in small numbers of animals, using antirabbitkidney hen sera. Since the results were identical in every respect they will not be described in detail.

In order to further confirm these findings, the technique of fluorescein-

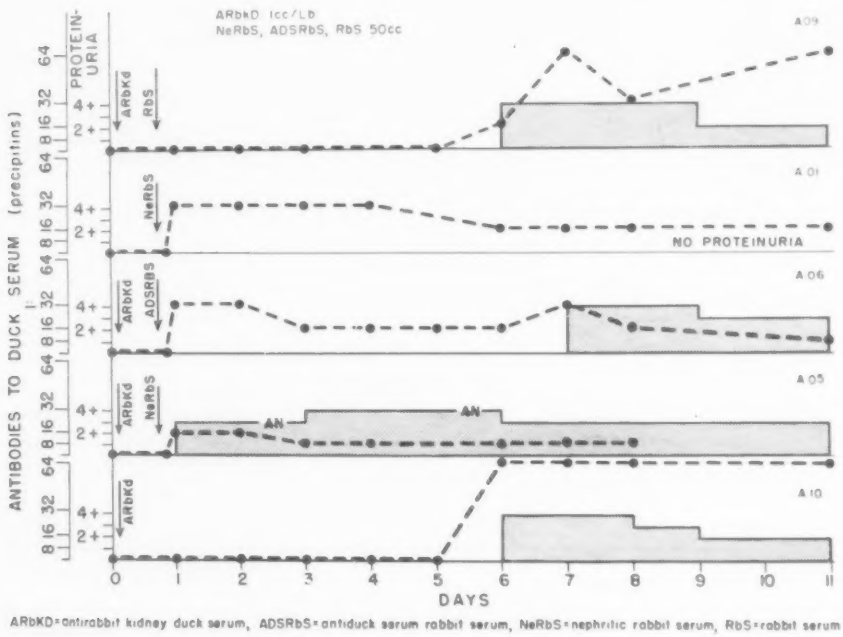


Fig. 2.—Influence of the transfusion of nephritic rabbit serum and antiduckserum rabbit serum on the appearance of proteinuria and antiduckserum titers in rabbits sensitized with antirabbitkidney duck serum

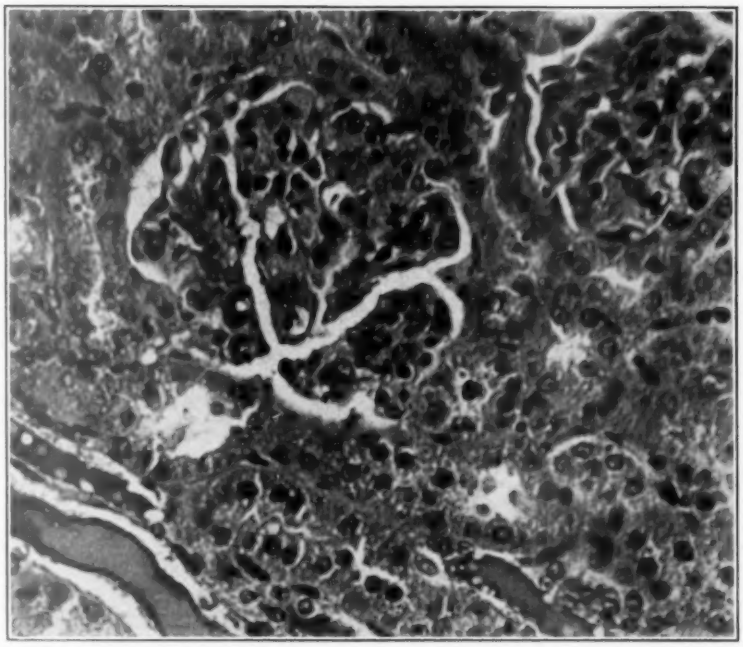

Fig. 3.—Acute glomerulonephritis in a rabbit sensitized with antirabbitkidney duck serum and transfused with 50 ml. of nephritic rabbit serum 24 hours later, sacrificed 6 hours after transfusion. Hematoxylin-eosin stain, × 260.

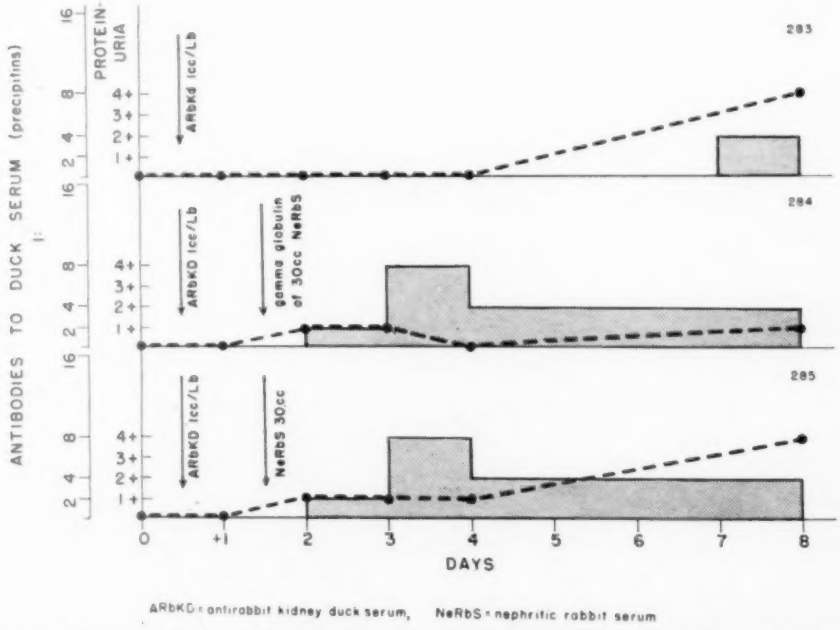


Fig. 4.—Influence of the transfusion of the gamma globulin fraction of nephritic rabbit serum on the appearance of proteinuria and antiduckserum titers in rabbits sensitized with antirabbitkidney duck serum.

labeled antibodies was used. When kidneys of normal rabbits were stained either with fluorescein-labeled globulin fractions of nephritic rabbit serum or antiduck serum rabbit serum or antirabbit gamma globulin duck serum no fluorescence was noted.

When rabbits were given ARbKDS (1 ml. per lb.) and were sacrified 24 hours later and sections of their kidneys stained with the 3 fluorescein-labeled antibodies mentioned above, the following results were obtained.

Staining with antirabbit gamma globulin did not produce fluorescence.

Staining with antiduck globulin rabbit globulin led to a very weak fluorescence of the glomeruli, most prominently of the basement membrane.

Staining with the globulin of nephritic rabbit serum led to an intense staining of almost all glomeruli, most strikingly of the basement membrane.

Staining after preabsorption with a nonfluorescent antibody followed by the same antibody but fluorescein labeled as a control did not show any fluorescence.

The kidneys of 2 animals sacrificed 2 hours after the injection of the sensitizing dose of ARbKDS showed identical staining pattern although the staining in the instances where it was positive was not as intense as after 24 hours.

Rabbits sacrificed on the second, third and fourth day after the original injection of ARbKDS showed the same behavior but the staining was more brilliant. All these animals did not show proteinuria or morphologic abnormalities on routine sections (Wachstein and Lange[23]).

Starting on the fifth or sixth day, whenever proteinuria appeared or a few hours before, serum complement fell precipitously and staining with fluorescein-labeled antirabbit gamma globulin produced fluorescence of the basement membrane of the glomeruli which became more intense as the days of active disease went on. Animals sacrificed on the fourth or fifth day often showed small but clearly distinguishable sickle-shaped areas of fluorescence in the basement membrane when stained with antirabbit gamma globulin duck serum. These animals did not have an abnormal proteinuria as yet. Simultaneously with the appearance of the staining by antirabbit gamma globulin and appearance of disease, staining with fluorescein-labeled globulin of nephritic rabbit sera decreased very markedly and disappeared completely after 2 to 3 days and remained negative thereafter. The fluorescence of the glomeruli when stained with labeled antirabbit gamma globulin remained intense for weeks after the onset of disease, whether or not clinical healing as documented by loss of proteinuria and return of serum complement and BUN to normal occurred. An animal sacrified 388 days after the initial onset of experimental glomerulonephritis and 365 days after proteinuria had disappeared still showed strong staining with antirabbit gamma globulin. Even glomeruli which were completely fibrosed due to the previous disease still showed punctate fluorescence throughout the fibrotic tissue.

**Discussion.** The data presented seem to indicate that the antibody producing experimental glomerulonephritis is specifically directed against the localizing fraction of the ARbKDS and is not an antibody against unmodified duck serum. It would appear that the ingenious theory of Kay about the modality of experimental glomerulonephritis produced by avian sera should be modified accordingly. Kay's experiment[8], in which he injected rabbits with duck serum and after several

weeks reinjected them with ARbKDS and obtained an immediate rise in antiduck serum titers as an anamnestic reaction without immediate appearance of disease, seems to corroborate these findings. The ability to produce experimental glomerulonephritis immediately upon passive transfer of antibodies against ARbKDS from a nephritic animal into an animal sensitized 24 hours before by an injection of ARbKDS and the inability to obtain the same result by the transfusion of antibodies against unmodified duck serum indicated the high specificity of the antibody which is directed against the localizing fraction rather than against unmodified duck serum (Fig. 5). ARbKDS as well as the disease producing antibody in nephritic rabbit serum are contained in the globulin fraction and the use of only this fraction for the production of experimental glomerulonephritis is recommended to reduce the number of immunologic side reactions especially the production of antibodies against albumin. The constant interval between the injection of ARbKDS and the appearance of disease found in all our animals also indicates that an antibody has to be formed by the recipient animal to produce disease. This is in contrast to the experimental kidney damage produced without delay in mammals by mammalian antikidney serum. The latter is a true nephrotoxic serum, while avian antikidney sera set up an active immune reaction in the recipient with formation of his own antibodies and are, therefore, not truly nephrotoxic. We suggest that the disease produced in mammals by mammalian antisera be called monophasic experimental nephritis while the dis-

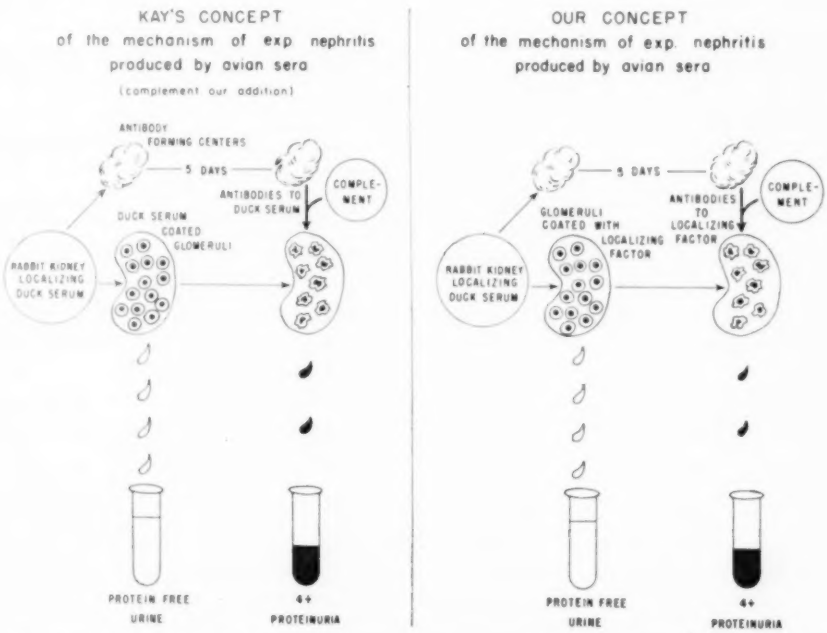


Fig. 5.—Kay's[8] concept of the mechanism of experimental glomerulonephritis produced by antirabbitkidney duck serum contrasted to our concept of the mechanism.

ease produced in mammals by avian kidney localizing sera be called biphasic experimental glomerulonephritis.

In addition an experimental glomerulonephritis of short duration can be produced by antigen-antibody reactions (Schwab *et al.*[20]) to nonlocalizing foreign proteins, for example, beef gamma globulin and beef albumin. Dixon *et al.*[4] have recently studied the immunologic mechanism of this type of disease and found with the fluorescein-labeling technique that such an antigen as beef gamma globulin does not localize on the glomeruli. Only when antibody against the beef gamma globulin appears in the circulation and joins with the antigen in the blood stream, the antigen-antibody complex localizes in the kidney possibly in the process of excretion and can be found there with the fluorescein-labeling technique. Thus a third mechanism only very remotely related to the human disease can produce transitory renal damage.

The results described above indicate that there is practically an immediate union between the injected ARbKDS and the glomerular basement membrane. This confirms the findings of Pressman, Korngold and Heymann[19] based upon similar experiments, but using the radioactive iodine-labeling technique.

There is a much more intense staining of the glomeruli when nephritic rabbit serum is used than when plain antiduck serum of a similar titer is used. This confirms our other experimental evidence that it is actually the localizing factor which adheres to the glomeruli and not to any large extent unmodified duck serum.

Our complete inability to obtain any evidence of localization of gamma globulin on the glomeruli prior to the fourth, or more commonly the fifth day after the injection of the ARbKDS seems to corroborate the disease mechanism as suggested in Fig. 5.

The rapid disappearance of the ability to stain with fluorescein-labeled nephritic rabbit sera after appearance of the clinical disease appears of significance. It is best explained by the fact that with the appearance of disease the rabbit produces antibodies against the localizing factor of the ARbKDS and that these antibodies rapidly saturate the sites of localization on the glomeruli. Thus the labeled antibody encounters an antigen which is already saturated with antibody and no additional union takes place. We are thus confronted with an *in vivo* example of the control experiment done in all fluorescein-labeled antigen-antibody reactions where, by preabsorption with a nonlabeled antibody of the same type, specific staining does not occur. This experience is of importance since it explains why attempts of staining with fluorescein-labeled globulins of nephritic sera in the kidneys of human cases of glomerulonephritis are probably doomed to failure on theoretical grounds. While we could confirm the report of Mellors and Ortega[17] of positive staining with fluorescein-labeled antihuman gamma globulin in human cases of nephritis we were so far unable to obtain specific staining with fluorescein-labeled nephritic sera.

**Summary.** 1. When antirabbitkidney duck or chicken serum was given to rabbits, the disease occurred with regularity after a minimum delay period of 4 to 5 days. When part of the antirabbitduck serum was replaced by unmodified duck serum there was as much delay in appearance of disease as if the smaller amounts of antirabbitkidney duck serum were given alone, although high antiduck serum titers appeared several days before the occurrence of disease.

Replacement of part of the anti-

rabbitkidney duck serum by human serum had the same effect as replacement by normal duck serum, although here the antiduck serum titers were very low.

Transfusion of nephritic rabbit serum to normal rabbits did not produce disease.

Transfusion of nephritic rabbit serum to rabbits previously sensitized with antirabbitkidney duck serum caused immediate disease.

Transfusion of serum of rabbits immunized with duck serum to rabbits previously sensitized with antirabbitkidney duck serum did not cause immediate disease.

2. The antibody, producing disease was, therefore directed specifically against the localizing factor not against normal foreign protein.

3. Experimental glomerulonephritis in rabbits was also produced with the globulin fraction of antirabbitkidney duck serum. Transfusion of the globulin fraction of nephritic rabbit serum had the same effect as transfusion of whole nephritic serum.

4. Fluorescein labeled antibodies against rabbit gamma globulin localized in the glomeruli when disease appeared but not during the delay period. Fluorescein labeled antibodies against duck serum and labeled nephritic rabbit serum localized immediately after antirabbitkidney duck serum was administered. Staining with the antiduck serum was weak, while staining with the nephritic rabbit serum was intense.

5. After disease appeared, the animals own antibodies against the localizing factor occupied the sites of the antigen, and staining with antiduck serum and nephritic rabbit serum did not occur.

6. Since nephritis in mammals following injection of avian antisera (not truly nephrotoxic) is caused by the antibody produced by the recipient animal, as evidenced among other facts by the delay period, it should be called biphasic disease. In contrast, mammalian antisera produce immediate nephritis in mammals by direct nephrotoxic action. This disease should be called monophasic.

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## SUMMARIO IN INTERLINGUA

### Le Mechanismo De Glomerulonephritis Experimental, Producite In Conilios Per Avian Seros Anti-Ren

1. Quando sero anti ren de conilio, ab anate o gallina esseva administrate a conilios, le morbo occurreva con regularitate post un intervallo minimal de 4 a 5 dies. Quando un parte del sero de anate anti ren de conilio esseva reimplaciate per sero de anate non modificate, le retardo in le manifestation del morbo esseva le mesme como si solmente le sero de anate anti ren de conilio (in le quantitate reducite) habeva essite administrate, ben que alte titros de sero anti anate appareva plure dies ante le declaration del morbo.

Le reimplaciamento de un parte del sero de anate anti ren de conilio per sero human habeva le mesme effecto como su reimplaciamento per sero de anate non modificate, ben que in iste caso le titros de sero anti anate esseva multo basse.

Le transfusion de sero ab conilios nephritic a conilios normal non produceva le morbo.

Le transfusion de sero ab conilios nephritic a conilios previemente sensibilisate con sero de anate anti ren de conilio causava le declaration immediate del morbo.

Le transfusion de sero ab conilios immunisate con sero de anates a conilios previemente sensibilisate con sero de anate anti ren de conilio non causava un morbo immediate.

2. Ergo le anticorpore que produceva le morbo esseva dirigite specificamente contra le factor localisante non contra un normal proteina alien.

3. Glomerulonephritis experimental esseva etiam producite in conilios per medio del fraction globulinic de sero de anate anti ren de conilio. Le transfusion del fraction globulinic de sero de conilios nephritic habeva le mesme effecto como le transfusion de sero complete de conilios nephritic.

4. Anticorpore anti globulina gamma de conilio, quando marcate con fluoresceina, se localisava in le glomerulos si tosto que le morbo appareva sed un durante le precedente periodo de retardo. Anticorpore anti sero de anate, con marcation per fluoresceina, e sero de conilio nephritic, similemente marcate, se localisava immediatemente post le administration de sero de anate anti ren de conilio. Coloration de leve grados resultava de sero anti anate, durante que coloration intense resultava de sero de conilio nephritic.

5. Post que le morbo appareva, le anticorpores del animales mesme contra le factor localisante occupava le sito del antigeno, e coloration con sero anti anate e con sero de conilio nephritic non occurreva.

6. Viste que nephritis in mammales post le injection de antiseros avian (non vermente nephrotoxic) es causate per le anticorpore producite per le animal receptori—iste facto es evidentiate per varie observationes, incluse le periodo de retardo—illo deberea esser designate como un morbo biphasic. Per contrasto, antiseros mammalian produce in mammales un nephritis immediate per lor directe action nephrotoxic. Iste morbo deberea esser appellate monophasic.

# THE PROPHYLACTIC USE OF SULFAMETHOXYPYRIDAZINE (KYNEX) DURING A STREPTOCOCCAL EPIDEMIC*

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Reports of the favorable pharmacologic properties of sulfamethoxypyridazine (Boger *et al.*[1], Nichols and Finland[7] and Roepke, Maren and Mayer[9]) have been followed by clinical studies suggesting the usefulness of this drug in a variety of therapeutic situations (Grieble and Jackson[3], Prlina, Dahlen and Bischoff[8], Sanchez *et al.*[10] and Walker and Hamburger[14]). One of the outstanding properties attributed to this drug by all investigators has been the production of prolonged elevated blood sulfa levels following single oral doses. Finland, Jones, Ziai, and Cherrick[2] have suggested that a single weekly dose of 30 mg. per kg. might be adequate for the prophylaxis of rheumatic patients against streptococcal infections. In a preliminary trial, Lepper, Simon and Marienfeld[5] reported satisfactory results in patients placed on this regimen in a rheumatic home and clinic. Stollerman and Johnson[11] have made similar observations in a clinic where children were given 2 gm. once weekly. In both of these studies, evaluation of the drug was difficult because the streptococcal challenge to patients was minimal and control observations were not available.

The present study was undertaken to evaluate sulfamethoxypyridazine in doses of 2 to 3 gm. once weekly as an alternate agent in controlling the spread of streptococci among Navy recruits who are not able to receive benzathine penicillin. The acquisition of group A streptococci by Navy recruits under sulfamethoxypyridazine prophylaxis was compared with that in untreated controls. In addition, observations on the acceptability of the program and side effects of the drug were made.

**Materials and Methods.** POPULATION AND PLAN OF STUDY. Paired companies of Navy recruits (approximately 130 men) entering the Great Lakes Naval Training Center in the winter of 1957–1958 were scheduled to receive 600,000 units of benzathine penicillin as prophylaxis against streptococcal infections. A single intramuscular injection was given in the third to fifth week of training at the time of the last routine immunization. All recruits were screened for a history of penicillin sensitivity or other allergy and excluded from the benzathine prophylaxis at the discretion of the interviewing medical officer. Three hundred and twenty-seven men excluded from benzathine prophylaxis became part of the present study. Groups of these men were randomly designated for treatment or as controls. Two men in the treated group reported

*From Research Project NM 52 06 04.11, the Bureau of Medicine and Surgery, Navy Department, Washington, D.C. The opinions and assertions expressed herein are those of the authors and cannot be construed as indicating endorsement or approval by the Navy Department or the Naval Service at large.

a history of sulfa sensitivity and were excluded from the study.

After the men were informed of the general scope of the study, initial throat cultures were obtained, and thereafter, cultures were repeated at least once weekly. Since the efficacy of the drug was determined by the isolation of group A streptococci, a placebo control was considered unnecessary. Men in the treated group were instructed to swallow tablets at one time with water before retiring on the day the drug was distributed, and to maintain a high fluid intake. They were alerted to the possibility of reactions. They were warned that periodic urine specimens would be tested to see if the drug was actually taken.

Fifty-seven men were given 2 gm. of sulfamethoxypyridazine (Kynex*) each week; 122 men were given 3 gm. weekly doses. The drug was delivered weekly to the barracks in individual packets printed with instructions and the man's name. Interviews were conducted to determine compliance with the program and side effects of the drug.

BACTERIOLOGY. All throat swabs were transported to the laboratory in sterile tubes and streaked on sheep blood agar plates within one hour. Each was subsequently processed by standard techniques used for the isolation and serological identification of streptococci as reported elsewhere (Levinson and Frank[6]). Eighty-six strains of group A streptococci that were isolated during the study were tested for sulfa sensitivity by the method of Wilson[15].

BLOOD AND URINE ANALYSES. One hundred and eight urine samples and 65 heparinized blood specimens for white cell counts were obtained at random from the treated men. In addition to routine urinalysis, a qualitative "spot test" for sulfa was performed (Helper[4]).

**Results.** BACKGROUND INFORMATION. Only a brief outline of the year's experience will be presented here to indicate the over-all characteristics of the streptococcal problem as it relates to the present study. Two weeks after the peak incidence of Asian influenza in October, 1957, there was noted increasing illness related to streptococci and an elevated carrier rate for group A organisms throughout recruit training companies. The intensity of the epidemic was reflected in the admission to the hospital of 14 cases of rheumatic fever prior to the institution of mass penicillin prophylaxis in late December. Thereafter, there was a continued, relatively constant carrier rate of group A streptococci among men excluded from, or those not yet scheduled for, penicillin prophylaxis.

In Fig. 1, the isolation rates of group A streptococci and the total number of men observed in control and treated groups are plotted by weeks of the study. The rates in either group include men with positive culture as they entered the study as well as those who subsequently carried or acquired streptococci. The sharp peak observed in the week of February 22 among controls, therefore, is merely a result of the number of men entering the study who harbored streptococci in addition to the chance occurrence of many positive cultures among men already in the study during that week. These data do not relate directly to the efficacy of the drug, but are presented only to indicate that both groups were continually exposed to streptococci under conditions of high risk.

DRUG EFFECTIVENESS. Table 1 summarizes data relating to the effectiveness of sulfamethoxypyridazine in the two dosage schedules in preventing the acquisition of group A streptococci. Figures in bold type are statistically significant ($p<.05$). Criteria for acquisition were established and applied equally to treated and control men. In its strictest sense, an acquisition was considered to have occurred if a group A streptococcus was isolated from a man whose initial throat culture was negative. In addition, men who were initially positive were considered to have acquired a new organism if there was a change in the specific type of streptococcus subsequently isolated. It is evident from this table that men in

*Supplied by Lederle Laboratories Division, American Cyanamide Co.

the treated group were protected from acquiring streptococci by either of these criteria. The reduction in total acquisitions for all treated men in the study was highly significant ($p<.01$). However, the data for the 2- and 3-gm. segments of the study, when each is analyzed individually, show a trend toward protection, but are insufficient to be statistically significant. Table 1 also shows that approximately 14% of the 325 men were positive for group A streptococci on entering the study. Spontaneous reversion to negative or

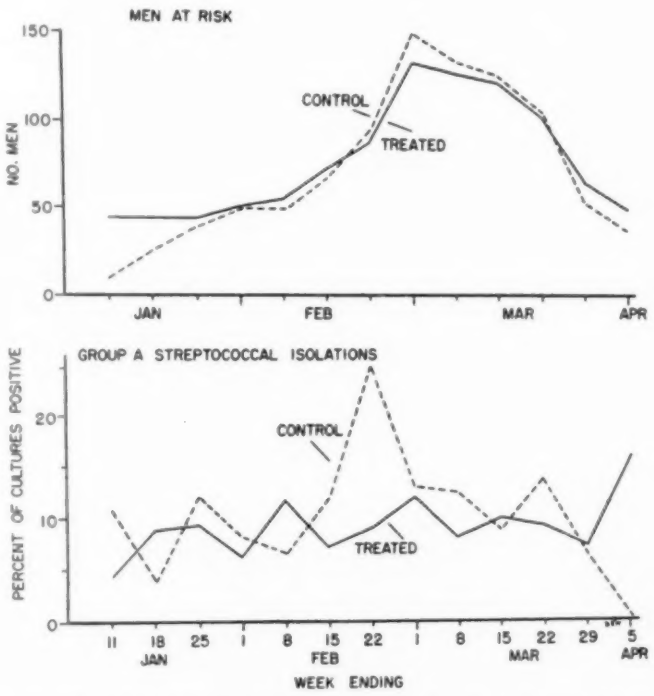


Fig. 1.—Men at risk and streptococcal isolation rates of sulfamethoxypyridazine treated and control groups by week of study.

TABLE 1.—ACQUISITION OF GROUP A STREPTOCOCCI IN CONTROL AND KYNEX TREATED MEN.

| | *2 gm. dosage* | | | | *3 gm. dosage* | | | | *Total* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Control* | | *Kynex* | | *Control* | | *Kynex* | | *Control* | | *Kynex* | |
| | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* |
| Men in group | 49 | 100.0 | 57 | 100.0 | 122 | 100.0 | 97 | 100.0 | 171 | 100.0 | 154 | 100.0 |
| Positive at start | 4 | 8.2 | 7 | 12.3 | 24 | 19.7 | 13 | 13.4 | 28 | 16.4 | 20 | 13.0 |
| Negative at start | 45 | 91.8 | 50 | 87.7 | 98 | 80.3 | 84 | 86.6 | 143 | 83.6 | 134 | 87.0 |
| Total acquisitions | 8 | 16.3 | 3 | 5.3 | 19 | 15.6 | 7 | 7.2 | **27** | 15.8 | **10** | 6.5 |
| From neg. to pos.* | 6 | 13.3 | 3 | 6.0 | 14 | 14.3 | 5 | 6.9 | **20** | 14.0 | **8** | 6.0 |
| Change in type† | 2 | 50.0 | 0 | 0.0 | 5 | 20.8 | 2 | 15.4 | 7 | 25.0 | 2 | 10.0 |

*Percentages based on those initially negative.
†Percentages based on those initially positive.

the persistence of organisms in two or more consecutive cultures occurred with equal frequency in both groups. Acquisition of a new type of streptococcus, on the other hand, was more common among men who did not receive the drug.

One untreated recruit, who acquired a streptococcus, had a past history of rheumatic fever and was, accordingly, ordered to the dispensary for treatment. No cases of acute rheumatic fever occurred among the men in the study.

ACCEPTABILITY OF THE PROGRAM. In general, treated men were found to be cooperative in complying with the prophylactic regimen, possibly because of the close contact between them and our research staff. Nevertheless, virtually all of the possible variations from the prescribed program were encountered in routine questioning of individuals during the study. Deviations included men who lost or neglected to take their tablets. One man saved up a week's supply and took a double dose the following week without ill effect. It is of some interest that neglect to follow the prescribed prophylactic regimen was noted at some time in 4 (44.4%) of the 9 men who represent failures of prophylaxis, in contrast to only 20 (13.8%) of the 145 men who did not acquire streptococci. Thus, acquisition of streptococci may have resulted more often from failure to adhere to the program than from inability of the drug to protect.

REACTIONS AND DRUG RESISTANCE. The reactions and side effects observed in treated men are shown in Table 2. The drug was administered weekly for 3 to 6 weeks depending on training schedules. Reactions were reported in 7.1% of treated men. Severe reactions consisting of fever, urticaria and rash, which required active treatment and complete discontinuation of the drug, occurred in 2 (1.3%) of the 154 men. Three of the 4 men who reported evanescent rashes were observed for 1 week and did not report a recurrence when the drug was again administered. Somnolence and headache were not prominent, possibly because the medication was taken before retiring.

There was no evidence indicating renal damage in the 110 random urine specimens examined. Crystalluria was observed in 3 instances. Typical "whetstone" crystals (Fig. 2) were seen in the urine of a recruit on the sixth day following a 3-gm. dose of drug. He was advised to increase his water intake, continued on the drug, and a subsequent urine was positive for sulfa, but did not contain crystals. Two other men passed crystals (one on the second and the other on the third day after taking the last dose of the drug) but could not be followed further. The white blood cell count in 65 blood specimens obtained at random was never less than 3,800 and routine hematology of the 2 men with severe reactions was not abnormal.

TABLE 2.—TOXIC REACTIONS AND SIDE EFFECTS IN 154 MEN ON WEEKLY DOSES OF SULFAMETHOXYPYRIDAZINE (KYNEX)

| *Condition* | *No. of Men* |
|---|---|
| Severe reaction (fever, urticaria, rash) | 2 |
| Evanescent rash | 4 |
| Nausea and vomiting | 2 |
| Headache | 3 |
| Total | 11 (7.1%) |

Eighty-six strains of group A streptococci that were isolated during the period of the study were screened for sulfa sensitivity. Two sulfa resistant strains were obtained from untreated individuals. None of the 33 strains from treated men were found resistant. There was no indication, therefore, that sulfa resistance had been induced by the use of sulfamethoxypyridazine.

potential candidates for rheumatic fever. In addition, approximately 10% of the men are unable to take penicillin following an episode of acute rheumatic fever and instead, must be placed on daily oral antibiotic prophylaxis.

This study indicates that weekly doses of sulfamethoxypyridazine (Kynex) are an effective prophylactic

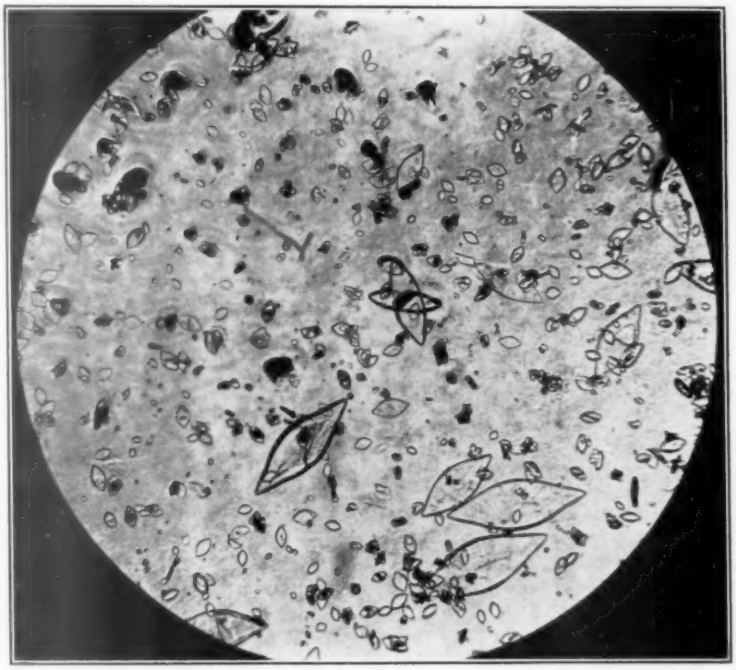

Fig. 2.—Urine sediment showing typical "whetstone" acetylsulfapyridine crystals.

**Discussion.** The need for another long-acting preparation useful in streptococcal prophylaxis of individuals who cannot be given penicillin is well established. Experience in this laboratory indicates that under epidemic conditions, even small numbers of men who are not under effective streptococcal prophylaxis may act as a nidus for reactivation of the epidemic when prophylaxis is discontinued, and are

measure against streptococci. The drug was evaluated under conditions of high streptococcal prevalence when control observations were possible. All of the deficiencies inherent in a program which relies on patient understanding and cooperation in taking oral drugs were encountered in this brief but conclusive study. Seemingly, men will neglect a weekly medication as readily as one given daily, but,

under properly supervised conditions, the weekly administration of this agent is considered convenient and effective. From previous studies, a 2 or 3 gm. oral dose of sulfamethoxypyridazine would be expected to provide significant blood levels for at least 5 to 7 days. Although, once acquired, a streptococcus cannot be eradicated by this drug, it is possible that the presence of adequate blood sulfa levels can prevent frank infection and rheumatic fever even in men who become carriers.

Toxic reactions were not prominent in our series. All evidence to date indicates that sulfamethoxypyridazine is potentially capable of producing the same kind of toxic reactions seen with older sulfa preparations (Vinniconde[13]). The over-all incidence of severe reactions is not known, but isolated cases have been reported (Tisdale[12]). The potential hazards of untoward reactions to sulfamethoxypyridazine must be considered prior to its use as a prophylactic agent. Because of the ease of administration and its prophylactic effectiveness, however, this drug can be recommended for use among penicillin-sensitive individuals when streptococcal prophylaxis is indicated.

**Summary.** The prophylactic effectiveness of sulfamethoxypyridazine (Kynex) during a streptococcal epidemic was studied among 325 Navy recruits excluded from penicillin prophylaxis. Compared to untreated controls, 154 men who were given 2 or 3 gm. of the drug once weekly were significantly protected from acquiring group A streptococci. Side effects of the drug were reported by 7.1% of treated men, but only 1.3% (2 men) had reactions considered severe. Sulfamethoxypyridazine can be recommended for use among penicillin sensitive individuals requiring streptococcal prophylaxis.

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## SUMMARIO IN INTERLINGUA

### Le Uso Prophylactic De Sulfamethoxypyridazina (Kynex) Durante Un Epidemia Streptococcal

Le efficacia prophylactic de sulfamethoxypyridazina (Kynex) durante un epidemia streptococcal esseva studiate inter 325 recrutas del Marina qui non recipeva penicillina prophylactic. In comparation con non-tractate subjectos de controlo, 154 del 325 recrutas, recipiente 2 o 3 g del droga un vice per septimana, se provava significativemente protegite contra le acquisition de streptococcos de gruppo A. Effectos lateral esseva reportate per 7,1% del subjectos tractate, sed illos esseva considerate como sever in solmente 1,3% (*i.e.* 2 del recrutas). Sulfamethoxypyridazina pote esser recommendate al uso como agente prophylactic antistreptococcal in subjectos qui es sensibile a penicillina.

# FIXED COMBINATION OF CHLOROTHIAZIDE-RESERPINE* IN HYPERTENSION

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Following the synthesis of chlorothiazide (Diuril) by Novello and Sprague[5], considerable interest was created in its diuretic properties. That the drug produced a marked increase in the urinary excretion of sodium, potassium and chloride was demonstrated in both animal pharmacologic studies (Baer, Leidy and Brooks[1]) and in human clinical trials (Ford *et al.*[2]). Two groups (Freis and Wilson[3], Hollander, Chobanian and Wilkins[4]) independently observed that the drug had, in addition to its diuretic properties, significant hypotensive effects. These hypotensive effects have been reported to occur both when the drug was used alone and when used in combination with other antihypertensive agents.

The precise mode of action of chlorothiazide as a hypotensive agent is not known. It may be that its effects on electrolyte excretion and redistribution offer part of an explanation, but certainly other factors, such as decrease in pressor substances, such as renin, must be considered. We have confirmed the earlier reports (Freis and Wilson[3], Hollander, Chobanian and Wilkins[4]) stating that chlorothiazide causes no significant reductions in the blood pressure of normal subjects, but were not as impressed as other investigators with its hypotensive effects when the drug was used without other hypotensive agents.

The "striking" and "selective" hypotensive effects of chlorothiazide reported by these investigators were not observed in our clinic. It should be pointed out that hypotensive effects have been attributed, often without sufficient clinical evidence, to other diuretic agents. Only in hypertensive patients in severe congestive failure have we observed hypotensive effects of diuretics, notably with mercurials, but such effects are temporary in nature and invariably the blood pressure returns to pre-treatment levels on continued administration of the drug.

Since we had been unable to elicit a satisfactory hypotensive response according to the criteria of Duncan in a significant number of patients, it was

*The material for this study was kindly supplied by John R. Beem, M.D., of Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania.

decided to determine whether the combined use of chlorothiazide with a hypotensive might offer therapeutic advantages.

**Methods and Materials.** This study consisted of a group of 24 patients with essential hypertension and one with chronic glomerulonephritis treated on an outpatient basis in the Cardiac Clinic of the St. Barnabas Medical Center, Newark, New Jersey. Severity index, according to the criteria of Duncan, was at least Grade II in all patients. Controls were established by taking the average of a minimum of six separate blood pressure and pulse rate determinations in the supine and upright positions.

During therapy patients were observed at least once weekly and, in many instances, daily. Pressures were taken in both the supine and upright positions.

Most of the patients had been receiving a ganglionic blocking agent (mecamylamine) either alone or with reserpine, digitalis, and an oral mercurial diuretic (chlormerodrin). Their ages ranged from 35 to 70. We were provided with tablets containing 500 mg. of chlorothiazide and 0.125 mg. reserpine which did not permit much flexibility of dosage. Dosage varied from patient to patient, but the average was one tablet twice a day. Most of the patients had been under our care and observation for several years prior to the administration of this medication. During this study they were under observation for 4 months.

**Results.** Using the criterion for response a reduction in the mean blood pressure of 20 mm. Hg or more or a return to normotensive levels, the overall response rate to combination therapy of chlorothiazide and reserpine was 54%. During the course of therapy with chlorothiazide alone, only 12 out of 129 patients showed a significant response. The results are not as good as the 70 to 75% response rate we had previously observed with mecamylamine in this same group of patients. Table 1 lists in summary form average blood pressures before and during therapy. Figure 1 graphically summarizes the comparative results of various agents on a hypertensive patient.

During the course of this study, no specific electrocardiographic changes were evidenced. These patients had been well controlled and free of the signs and symptoms associated with congestive heart failure prior to therapy and they were uniformly maintained in this satisfactory state.

In no instance was there a serious drop in the serum levels of sodium, potassium and chloride. It thus appears that the hypotensive effects are probably not due to sodium depletion. It may be that chlorothiazide delays the excretion of the hypotensive agent thus permitting more prolonged and more marked pressure reductions. This is illustrated well in Fig. 1. This patient had been on mercuhydrin, iproniazid and reserpine at various times with only iproniazid showing a significant hypotensive effect. With chlorothiazide alone no hypotensive effect was evidenced, but with increasing doses of reserpine and chlorothiazide, a pronounced drop in blood pressure occurred.

SIDE EFFECTS. In the patients reported in this study no significant side effects were observed. The compound was well tolerated orally. Routine hemograms and urinalyses revealed no abnormalities after administration of the chlorothiazide for several months.

**Summary and Conclusions.** It is apparent from our data and that of other investigators that chlorothiazide is an effective diuretic agent. Certainly it appears to be at least as potent as the organic mercurials.

While several investigators have demonstrated significant hypotensive effects with chlorothiazide, we have not been as impressed as they. Admittedly, chlorothiazide does have mild hypotensive effects in some patients, but such effects do not occur frequently enough and are not marked enough to warrant the routine use of chloro-

thiazide for the treatment of hypertension. It is significant to note, however, that normotensive patients do not show any hypotensive responses to the drug.

Based upon our experiences to date, it does appear that chlorothiazide is a useful drug when used in combination with other hypotensive agents. We do not believe that its effects are related to alterations in salt metabolism alone, but may possibly be due in part to a direct hypotensive action. It is entirely possible that the apparent potentiating effect sometimes observed when chloro-

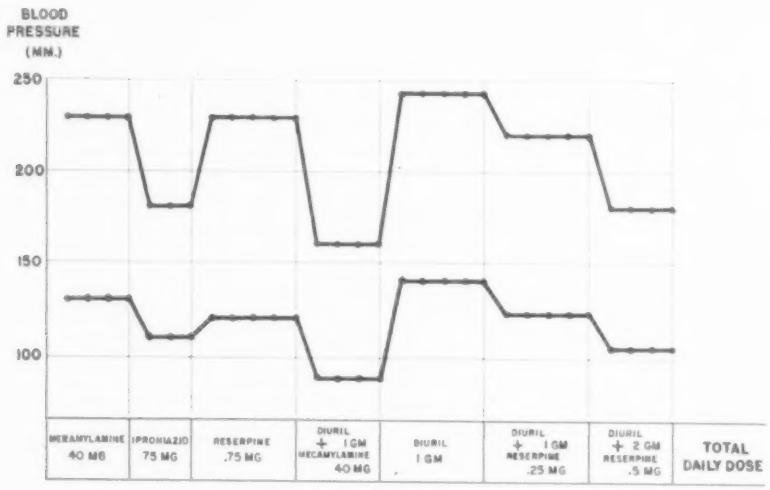


Fig. 1

TABLE 1.—AVERAGE BLOOD PRESSURES BEFORE AND DURING THERAPY

| *Case No.* | *Before Therapy* | *Diuril-reserpine* | *Mean Reduction in Blood Pressure* |
|---|---|---|---|
| 1 | 180/135 | 150/100 | 45 |
| 2 | 170/128 | 150/100 | 26 |
| 3 | 175/120 | 158/116 | 5 |
| 4 | 180/110 | 160/90 | 20 |
| 5 | 175/110 | 160/106 | 4 |
| 6 | 210/140 | 208/138 | 0 |
| 7 | 190/110 | 130/80 | 40 |
| 8 | 175/102 | 170/95 | 0 |
| 9 | 170/120 | 160/114 | 9 |
| 10 | 180/120 | 165/110 | 12 |
| 11 | 210/130 | 185/100 | 27 |
| 12 | 160/115 | 130/90 | 29 |
| 13 | 204/135 | 155/100 | 40 |
| 14 | 250/138 | 248/135 | 0 |
| 15 | 235/135 | 195/100 | 35 |
| 16 | 180/110 | 140/90 | 26 |
| 17 | 175/100 | 170/95 | 5 |
| 18 | 225/130 | 185/110 | 28 |
| 19 | 210/120 | 165/115 | 20 |
| 20 | 175/120 | 150/110 | 12 |
| 21 | 185/125 | 160/115 | 15 |
| 22 | 180/130 | 160/110 | 17 |
| 23 | 190/90 | 145/76 | 25 |
| 24 | 200/120 | 155/105 | 22 |

thiazide is administered with another hypotensive agent may be due to a delay in excretion of the hypotensive agent caused by chlorothiazide.

Certainly chlorothiazide offers many advantages both as a diuretic agent and as a hypotensive in patients with congestive heart failure. It is well tolerated, effective, and has been singularly free of serious side effects thus far.

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## SUMMARIO IN INTERLINGUA

### Chlorothiazido E Reserpina In Combination Fixe In Le Tractamento De Hypertension

Es evidente ab nostre datos e ab le datos de altere investigatores que chlorothiazido es un efficace agente diuretic. Illo certo pare esser al minus tanto potente como le mercuriales organic.

Durante que plure investigatores ha demonstrate significative effectos hypotensive de chlorothiazido, nos ha non essite impressionate in iste senso. Il debe esser admittite que chlorothiazido ha leve effectos hypotensive in certe patientes, sed tal effectos non occurre satis frequentemente e non es satis marcate pro justificar le uso routinari de chlorothiazido in le tractamento de hypertension. Tamen, es significative notar que patientes normotensive non monstra ulle responsa hypotensive post le administration del droga.

Nostre experientias usque al tempore presente pare supportar le assertion que chlorothiazido es un droga utile quando illo es usate in combination con altere agentes hypotensive. Nos non crede que su effectos es relationate a alterationes in le metabolismo de sal per se, sed il pare possibile que illos resulta in parte directemente ab un action hypotensive. Il es etiam completemente possibile que le apparente effecto potentiatori que es observate a vices quando chlorothiazido es administrate in combination con un altere agente hypotensive resulta del facto que chlorothiazido retarda le excretion del agente hypotensive.

Sin dubita, chlorothiazido offere multe avantages tanto como agente diuretic como etiam como agente hypotensive in patientes con congestive disfallimento cardiac. Illo es ben tolerate, efficace, e frappantemente libere de serie effectos lateral, al minus in su applicationes usque al tempore presente.

# PROGRESS
# OF
# MEDICAL SCIENCE

## PEDIATRICS

UNDER THE CHARGE OF

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## HYPOTHYROIDISM AND GOITER DUE TO DEFECTS IN THE INTRATHYROIDAL SYNTHESIS OF THYROXINE

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IN 1897, Osler[24] reported 60 cases of sporadic cretinism throughout the United States. Seven of these cases had goiters and, in one family, 3 of 5 children had a goiter associated with cretinism. Subsequently, numerous instances of hypothroidism and goiter have been reported. Hamilton *et al.*[11], in 1943 reported the occurrence of goiter in 2 patients with hypothyroidism in which the uptake of $I_{131}$ was elevated. In 1946, Lerman, Jones and Calkins[19] studied 2 hypothyroid brothers who lived in a nongoitrous region and who had developed goiters at 5 and 12 years. When removed, the thyroid glands showed marked hyperplasia. In 1950, Stanbury and Hedge[34] published a report of their now famous family of goitrous cretins. They described 3 siblings with goiter, all of whom were hypothyroid. They were shown rapidly to accumulate large amounts of radioiodine in the thyroid which was promptly discharged following administration of oral potassium thiocyanate. They concluded that the siblings could trap iodine normally but could not convert it to thyroxine.

Hubble[15], in 1953, described 4 siblings with hypothyroidism and goiter in one family. In the patient studied, the uptake of $I_{131}$ was elevated and thyroxine was isolated from the thyroid after its removal. The thyroid showed marked hyperplasia. He concluded that the thyroids of these siblings, although able to synthesize some thyroxine, were unable to synthesize adequate amounts, the result being hypo-

thyroidism. Compensatory hyperplasia of the thyroid was responsible for the goiter. In 1953, McGirr and Hutchison[21] reported studies on 12 nonendemic goitrous cretins. Seven were closely related, 2 were members of another family, and 3 were unrelated to either family or to each other. The thyroidal $I_{131}$ uptake and the protein bound $I_{131}$ studies in most of the patients were elevated. These investigators concluded that the thyroid glands of their patients were capable of incorporating iodine into an organic form and releasing it from the gland, but that the released compound was not thyroxine.

In 1954, Wilkins *et al.*[46] reviewed the previously reported cases and reported 4 additional cases, 2 of which were siblings. In one patient, iodine taken up by the thyroid was not discharged when potassium thiocyanate was administered. The thyroid glands of the siblings were not enlarged.

Although different in some respects, the 32 cases reported through 1954 had a number of features in common. In 19 there were multiple familial incidences suggesting genetic transmittance. Uptake studies revealed that the thyroids in those studied were capable of trapping normal or increased amounts of radioiodine. In no instance did any of the patients live in iodine deficient areas. Intense hyperplasia was revealed histologically in all the thyroid glands removed. Although all of the patients were classified as cretins, the age of onset of hypothyroidism, when known, varied considerably, as did the severity of the hypothyroidism and the size of the goiter. In the cases reported by Hubble[15], apparently the thyroids were capable of incorporating iodine into an organic form, whereas in the cases reported by Stanbury[34], the thyroid glands could trap iodine but apparently could not bind it organically, thus suggesting different defects in thyroxine synthesis. It would appear that common to all of these patients was the inability to synthesize normal amounts of thyroxine. This resulted in hypothyroidism and hyperplasia of the thyroid secondary to increased thyrotropin stimulation.

Subsequent to 1954, other reports of goitrous cretins have been published in which the findings were essentially the same as has been reviewed above[6,8,16,20,25,45,47]. In addition, there has been considerable clarification of the etiology of some of these defects. Advances in thyroid physiology have been numerous, and the use of radioiodine, the determination of the serum protein bound iodine, together with many other methodologic procedures have aided in defining these defects. Finally, rapid strides in the understanding and nature of these metabolic defects have come about in great part through the investigations of Dr. John Stanbury and his collaborators.

THE INTRATHYROIDAL SYNTHESIS OF THYROXINE. Iodine in food or water is reduced during the process of absorption and enters the thyroid as iodide. The thyroid, under the control of pituitary thyrotropin, traps and concentrates, by an unknown mechanism, large amounts of iodide where it is either enzymatically oxidized to iodine or is loosely bound to protein as inorganic iodide[42]. Cytochrome oxidase and peroxidase have been suggested as the enzymes which promote this oxidation. However, certain antithyroidal agents prevent the oxidation of iodide. As thiouracil is a peroxidase inhibitor[4,29] but does not inhibit cytochrome, peroxidase is favored as the possible agent. Iodide as it accumulates in the thyroid gland occupies the "thyroid space." This space changes considerably under various conditions and in pathological states. The conversion of iodine to an

organically bound form apparently occurs very rapidly. It was originally thought by Harington and Randall[14], that iodination of tyrosine in the 3 and 5 position occurred simultaneously with formation of diiodotyrosine. Subsequently, condensation of two molecules of diiodotyrosine resulted in the formation of thyroxine. More recent studies have shown the presence of monoidotyrosine[7] and triiodothyronine[10] in normal thyroid tissue and it is thought that monoiodotyrosine is the precursor of diiodotyrosine. The presence of triiodothyronine in thyroid may occur as the result of condensation of monoidotyrosine with diiodotyrosine or of the deiodination of thyroxine[27], although no thyroxine deiodinase has been demonstrated.

The formation of thyroxine by the condensation of two molecules of diiodotyrosine is thought to be an oxidative step and has actually been demonstrated chemically with hydrogen peroxide in alkaline solution[12]. It has been suggested that the iodination of tyrosine utilizes hypoiodate, both as a source of iodine and as an oxidizing agent[13], although its presence in the thyroid has never been demonstrated.

Many investigators have found it difficult to accept the condensation of two molecules of diiodotyrosine as occurring, and it has been suggested[27,31] that iodine is introduced into tyrosine after tyrosine has been incorporated into a formed protein. This would relegate the role of the iodotyrosines to that of storage and transport of iodine.

Iodotyrosines as well as iodothyronines are present in the thyroid as thyroglobulins. Recent studies indicate that 0.5% of the total iodine in the thyroid may be "free" thyroxine and the same amount, free diiodotyrosine[43]. This, however, does not exclude a loose protein bond. In spite of the evidence that thyroxine precursors may occur in the thyroid in an unbound state, neither mono- nor diiodotyrosine has been demonstrated in the blood or urine of normal individuals[18,30,40,41]. Roche *et al.*[28] have demonstrated a deshalogenase which deiodinates "free" mono- and diiodotyrosine but not thyroxine. The liberated iodine may then be utilized by the thyroid for the iodination of thyronine. Thyroid hormone is stored in the lumen of the acinus as colloid. Since colloid has a molecular weight of 650,000, its large-sized molecules cannot enter capillaries. Colloid is split into smaller constituents of which one is thyroxine, presumably by the action of a proteolytic enzyme which has been isolated from thyroid[5]. Though the manner of release of thyroxine has not been clearly defined, it is suggested that thyroxine is released free into the blood and then becomes bound to plasma protein.

TYPES OF DEFECTS. *Failure of Organification of Iodine.* The first cases of sporadic cretinism in which a specific metabolic defect was found were those reported by Stanbury and Hedge in 1950[34], and Stanbury in 1951[33]. They found that the thyroidal uptake of $I_{131}$ of these patients was rapid and high, but following administration of oral potassium thiocyanate there was an immediate discharge of iodine. The protein bound iodine was low. They concluded that the thyroid was unable to convert iodine to an organically bound form. Stanbury *et al.*[38] compared the metabolism of $I_{131}$ in a goitrous cretin who had this defect with individuals taking methimazole. They found that the goitrous cretin disposed of $I_{131}$ in a manner similar to the patients with the methimazole block. They further reported that the decline of iodine in thyroid and blood was governed by the renal clearance. The

thyroid gland when analyzed, contained practically no organically bound iodine, confirming the presence of a metabolic defect. Shultz *et al.*[32] have reported a similar case. It is generally felt that this defect is due to an absence of the enzymatic processes which cause oxidation of iodide to iodine, although conceivably it could be due to other enzymatic processes responsible for the organic binding of iodine.

*Absence of Thyrodial Deshalogenase.* In 1955, Stanbury, Kassenaar, Meijar and Terpstra[35] reported studies carried out on an adult with a congenital goiter who had been treated with thyroid powder since the age of 9 months. A younger sibling also had a goiter at birth, required thyroid medication at about 2 years of age, and was retarded mentally. The clinical signs of hypothyroidism were present and the protein bound iodine was 0.5 μg. per 100 ml. The uptake of radioiodine was rapid, reaching a maximum value of 74% at 2½ hours. There was then a rapid release of iodine so that at 24 hours, only 36% of the administered dose remained in the gland. When the radioiodine in the blood was measured following intravenous administration of 1 μg. of $I_{131}$, it disappeared rapidly from the blood for a 70-minute period but then began to rise again and reached a maximum concentration at 24 hours. During the phase when the blood iodine was rising, a large fraction of the $I_{131}$ was not precipitable with trichloracetic acid. Subsequently, paper chromatographic studies were carried out on blood samples taken after the administration of a large dose of $I_{131}$ and within 22 hours after giving the $I_{131}$ the thyroid was removed. Labeled mono- and diiodotyrosine appeared in the blood 2 hours after administration of the $I_{131}$. Labeled triiodothyronine and thyroxine were also present in the serum. A thiocyanate test done on the goitrous sibling revealed a rapid high uptake of $I_{131}$ but no discharge of radioiodine following thiocyanate administration.

When these 2 siblings as well as another patient with hypothyroidism and goiter were administered $I_{131}$ labeled mono- and diiodotyrosine intravenously, the compounds were found to be excreted in the urine unchanged, as compared to 15 normal individuals who almost completely deiodinated the administered compounds[36,37]. They then studied the ability of thyroid slices from the younger sibling to deiodinate labeled diiodotyrosine, and found no deshalogenase activity present in the gland[26].

They concluded that in these patients there was an inability to deiodinate mono- and diiodotyrosine completely. These substances were excreted in the urine and hypothyroidism and goiter resulted from a continuous loss of hormone precursors. It is probable that the cases of McGirr and Hutchison[22] belong in this group, since they reported that diiodotyrosine had been found in the blood and urine of one of the members of a family with goiter and hypothyroidism. Kunstadter *et al.*[17] also reported a series of goitrous cretins, one of whom had diiodotyrosine in the plasma, but urinary studies and deshalogenase activity of the thyroid were not performed.

*Defect in Coupling of Diiodotyrosine or Defect in the Normal Formation of Thyroxine.* In 1957, Werner, Block, Mandel and Kassenaar[44] reported studies done on a 5-year-old Negro girl with a congenital goiter and mild hypothyroidism. She had marked elevation of the PBI ranging from 17 to 28 μg. per 100 ml. The uptake of $I_{131}$ was also markedly elevated on several occasions. Paper chromatographic studies on the blood following $I_{131}$ administration revealed the presence of

monoiodotyrosine, diiodotyrosine, thyroxine, and triiodothyronine in equal amounts. When the thyroid was removed 9 months after the chromatographic studies only small amounts of thyroxine and triiodothyronine were found. Normal deshalogenase activity was found in the thyroid after removal and peripheral deshalogenase activity was also indicated by the disappearance of administered labeled diiodotyrosine from the blood and its absence in urine. They concluded that although some thyroxine could be synthesized there was a block in the oxidative coupling of diiodotyrosine and that this block was due to the lack of a specific oxidative enzyme. Stanbury *et al.*[38] and Stanbury and Querido[39] reported their studies on one of 2 goitrous sisters with hypothyroidism who had an elevated uptake of $I_{131}$. Thyroxine was demonstrable in the blood but in abnormally low concentrations. Studies on the removed thyroid revealed that large amounts of iodotyrosines were present in the thyroid gland. They also concluded that the coupling of diiodotyrosine was faulty. However, contrary to the findings of Werner *et al.*[44], increased levels of mono- and diiodotyrosine in the blood were not demonstrated. The 2 cases reported by Mosier, Blizzard and Wilkins[23] were also able to trap and organically bind iodine. Chromatographic studies of thyroid tissue from these patients revealed mono- and diiodotyrosine but only trace amounts of thyroxine. Chromatographic studies of plasma demonstrated absence of both iodotyrosines and iodothyronines suggesting again a defect in the coupling of diiodotyrosine or a defect in the formation of thyroglobulin.

*Other Defects.* DeGroot, Postel, Litvak and Stanbury[3] recently reported studies done on a patient with hypothyroidism and goiter with a PBI of 2 μg. per 100 ml. and a 24 hour radioiodine uptake of 57%. Intravenously administered labeled thyroxine and diiodotyrosine were metabolized normally. Thiocyanate failed to cause a discharge of trapped $I_{131}$. Labeled $I_{131}$ which appeared in the plasma was only partially extractable with acid-butanol. The butanol soluble fraction proved to be thyroxine and triiodothyronine and the butanol insoluble fraction, identified by means of starch block electrophoresis and ultracentrifugation, was an abnormal iodinated protein having the mobility of albumin. This protein was not precipitated by equine antihuman serum albumin. They concluded that this patient was either forming an abnormal thyroprotein in the gland, or that abnormal fractionation of thyroglobulin with release of metabolically inactive iodinated protein into the serum was occurring.

A euthyroid patient with a large goiter was recently studied[1] and found to have a markedly elevated uptake of $I_{131}$, a PBI of 9.5 μg. per 100 ml. and butanol extractable iodine of 9 μg. per 100 ml. Paper chromatography of the serum after administration of $I_{131}$ revealed no mono-or diiodotyrosine. But large amounts of labeled material having the mobility of thyroxine were found. Triiodothyronine was also identified. A biopsy of the thyroid revealed marked hyperplasia similar to that described in goitrous cretins. When the patient was given dessicated thyroid, there was a marked reduction in the size of his thyroid gland. Although the studies were inconclusive, they suggested that large amounts of butanol soluble material similar to thyroxine but metabolically less active were being released into the serum.

These cases point out the fact that enzymatic defects may probably occur at any step in the synthesis or release of thyroxine. Others undoubtedly will be described.

DEFECTS IN SYNTHESIS AS A CAUSE OF

SIMPLE GOITER. Because of the great variation in the severity of enzyme defects, it has been suggested[9] that instances of simple goiter may result from mild defects in thyroxine synthesis which could be compensated for by stimulation of the thyroid with thyrotropin.

A family of 6 siblings, 4 of whom had goiters and were euthyroid, has recently been described[2]. The 4 children with goiters all demonstrated rapid discharge of labeled iodine from the thyroid when thiocyanate was administered orally. It was concluded that although the siblings with goiters had a defect in the ability to organically bind iodine, it was not sufficiently severe to produce hypothyroidism when thyrotropin stimulation caused compensatory hyperplasia of the thyroid.

**Summary.** Hypothyroidism may occur from an enzymatic defect at any step in the synthesis of thyroxine. Three types of defects have been characterized: a lack of iodide oxidase; a loss of thyroxine precursors due to the absence of specific deshalogenase; and failure of thyroxine formation in spite of the formation of normal precursors. Other defects have been described but are less clearly defined. The presence of a goiter is common to all of these patients and is due to thyrotropin stimulation in an effort to compensate for abnormally low output of thyroxine by the thyroid. As in all diseases caused by defective enzyme systems, there is great variability in the severity of the hypothyroidism and it is thought that less severe defects may result only in the finding of a goiter.

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## GYNECOLOGY AND OBSTETRICS

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# PELVIC EXENTERATION IN CARCINOMA OF THE CERVIX
# A REVIEW OF THE LITERATURE

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FOR more than a decade, "ultra-radical" surgery has been utilized in an effort to control advanced pelvic malignancy. Brunschwig[7-15] performed his first pelvic exenteration in 1946, and has subsequently written extensively about this operation. Parsons *et al.*[21,22], Bricker *et al.*[3-6], Schmitz *et al.*[23,24], and Ulfelder and Meigs[25] have also undertaken pelvic exenteration and have published their results. Numerous important facts have been accumulated concerning this extensive operation. The purpose of this paper is to review the current status of pelvic exenteration as it applies to the management of the commonest cancer of the female pelvis, carcinoma of the uterine cervix.

Pelvic exenteration consists of the removal of all or part of the viscera that occupy the pelvis, the adventitious tissue, the peritoneum and the lymph nodes. Total exenteration refers to the removal of all of the pelvic organs from the brim of the pelvis to the vulva. The removal of the structures in the anterior portion of the pelvis with preservation of the rectum and sigmoid is spoken of as anterior exenteration, while a similar procedure, sparing the bladder and pelvic ureters, is named posterior exenteration. The last of these operations is usually disregarded in mortality and survival statistics, because it is considered to be simply a more extensive type of abdominoperineal resection. It also does not produce the significant physiological alterations associated with removal of the urinary bladder. Other terms which are used to describe these operations are, "Brunschwig," "All-American," "North American," "South American," multivisceral pelvic resection[26], and perineum-pelvic-panviscerectomy[19]. The term exenteration with the appropriate adjective appears to be quite adequate and sufficiently descriptive.

Although pelvic exenteration is being performed for malignant lesions of the endometrium, vulva, rectum, vagina, ovary, sigmoid and prostate, the results have been unsatisfactory generally. Parsons and Taymor[22] reported that only one patient lived beyond 2 years among 30 patients on whom pelvic exenteration had been done for cancer of either the endometrium,

ovary or rectum. By contrast, the results following pelvic exenteration for cervical cancer have been highly encouraging. Brunschwig and Daniel[13] reported a 15% five-year survival in 111 cervical cancer patients, and a 3-year survival of 22.4%. These patients were minimally selected. Parsons and Taymor[22] performed 86 exenterations for cervical cancer and found that 25.4% of 63 patients were living 2 to 6½ years later. They also reported a 25% survival among 28 patients who qualified for 5-year follow-up. In a review of 34 patients with cervical cancer, Schmitz *et al.*[24] reported a 2- to 5-year survival of 23.5%. It must be emphasized that most of these figures represent the results of pelvic exenteration following failure of primary therapy in the management of cervical cancer. Compared to the results of the primary treatment for cancer of the lung, pancreas, stomach, esophagus, and gallbladder, the above statistics are most commendable.

The pathological findings in patients who die from cervical cancer provide further evidence that this may be an ideal lesion for treatment by pelvic exenteration. Brunschwig and Pierce[16] reviewed the necropsy findings in 65 patients who succumbed to this disease and they found that 33 or 50% had no gross evidence of tumor beyond the pelvis. In 66% of these patients, uremia and infection were the immediate causes of death. The mortality due to uremia, based on postmortem study, has been reported to be 40% by DeAlvarez[17] and over 50% by Henriksen[20]. A recent report by Bartzen *et al.*[1], dealing with 58 patients who died of cancer of the cervix, also demonstrated that 44.4% died with the cancer limited to the pelvis, and that uremia accounted for 34.8% of the deaths. The tendency for cervical cancer to remain localized in the pelvis and produce death by metastasis to adjacent organs, contributes to the successful results noted previously. In addition, it helps to justify pelvic exenteration as a procedure which stands a reasonable chance of producing a cure in patients with advanced, recurrent, or radioresistant cervical carcinoma.

Routine mortality statistics are of little significance in evaluating pelvic exenteration as they are for more standard types of operation. Mortality figures from this operation are therefore broken down into 3 groups: surgical, hospital and total. Surgical mortality refers to death within 30 days of operation. Hospital mortality means that death occurred in the hospital beyond the 30-day limit, but that the patient was confined to the hospital from operation until death. The combination of surgical and hospital mortality is called the total mortality.

There has been a significant improvement in operative survival with the increase in the number of pelvic exenterations being performed. As the experience of the operator increases, similar improvement is noted. Brunschwig[7-9] initially reported a 23% mortality in his first 22 patients. He stressed the point that these early cases were not ideally selected. The patients were often in too poor condition to withstand such major surgical endeavors. In addition, the solution of numerous technical problems has reduced the operative risk. A later report by Brunschwig and Daniel[12] dealing with 315 operations for all types of lesions revealed a surgical mortality of 17.7% and a total mortality of 26.6%. Many patients, however, were still being operated upon with a view to palliation, so that many succumbed to their disease without leaving the hospital after operation. Parsons and Taymor[22] reported a total mortality of 28%, and they also noted that the mortality was directly related to the

extent of the procedure. They experienced a 9% mortality in partial exenteration and a 34% mortality in the total procedure. Schmitz *et al.*[24] reported their results in 34 patients. The total mortality in this group was 37.9%, with 61% for total, 35% for anterior, and 10% for posterior exenteration. Bricker *et al.*[3] had very commendable results in 118 total exenterations with a mortality of 13.5%. The early mortality in their series was 19.3% which later dropped to 8.2%.

The indications for pelvic exenteration in patients with cervical carcinoma may be placed into 4 categories: (1) Recurrence of extensive tumor following proper primary treatment by radiation or surgery. (2) Widespread lesions that demonstrate resistance to radiation therapy. (3) Stage IV (International Classification) lesions with extension to the bladder, rectum or both, but without lateral pelvic wall fixation. (4) Severe radiation necrosis resulting in fistulae or uncontrollable pain. Recently Brunschwig and Daniel[13] have done primary anterior exenterations on Stage II lesions with parametrial involvement and with encroachment upon the ureters. The use of a procedure of the magnitude of pelvic exenteration in these patients, where radiation alone will produce a 50 to 60% five-year survival with an insignificant risk, is open to some question.

A review of the indications for the use of pelvic exenteration in the management of cancer of the cervix, raises several points which deserve emphasis. The majority of individuals who are being considered for pelvic exenteration have had some previous treatment. The adequacy of such therapy must be evaluated, by a thorough review of the radiation dosage delivered to the pelvis by means of Roentgen ray, radium or both. Not infrequently the original treatment dosage is found to be inadequate, and additional radiation therapy may be added with successful results. In the same vein, if the primary effort was surgical, this treatment may have fallen short of radical hysterectomy with pelvic lymphadenectomy, and the persistent or recurrent tumor may respond to lesser measures than exenteration. The surgeon who performs pelvic exenterations should have a thorough understanding of the accepted primary treatment of cervical cancer, both by radiation and surgery. This will improve his ability to select patients who are suitable candidates for exenteration and consequently enhance his results. Often it is difficult even for the most experienced individual to make the proper decision. Necrosis and scarring due to radiation will mimic the picture of advancing tumor. An adequate biopsy should always be done to prove the existence of tumor. When the area of possible recurrence occupies the parametrium, it is usually impossible, short of laparotomy and excision biopsy of this region, to prove the presence or absence of active disease.

Radio-resistant lesions also present a troublesome group. At this writing, it is impossible to establish radioresistance in a cervical tumor without a full course of radiation therapy and observation of the clinical response that the lesion exhibits. This requires careful follow-up and repeat cytologic tests and biopsies of the tumor. The earlier that the lesion is determined not to be responding to radiation therapy, the more favorable the outcome will be following secondary treatment by pelvic exenteration. Should the resistant lesion be limited to the cervix or adjacent parametria, a lesser procedure, radical hysterectomy with pelvic lymphadenectomy, should be the procedure of choice. However, the delay caused by the time involved in

the radiation treatment and subsequent observation may allow the lesion to spread to the rectum or bladder so that any contemplated surgery, to offer any chance of cure, must of necessity entail the removal of one or both of these organs.

The results following radiation therapy for Stage IV cervical cancer have been so discouraging that primary pelvic exenteration deserves consideration. Whether preoperative radiation will improve the results has not been determined. When the bladder and rectum are invaded by tumor, one or both sides of the parametrium is likely to be fixed to the lateral pelvic wall. An effort to remove the lesion might result in transection of the tumor, thus leaving cancer-bearing tissue in the pelvis. In cases of this variety, preoperative radiation is worthy of consideration.

Patients who are suffering from severe radiation necrosis of the pelvic structures, with or without bladder or bowel fistulae, will often be helped by diversion of the urinary or fecal streams. In some, however, chronic discharge, inflammation and pain may still be troublesome. These individuals may experience a great improvement in general health following pelvic exenteration. Recognition must be given to the high mortality and morbidity which attend this operation, so that less drastic measures should first be attempted.

There has been, in recent years, a change in attitude toward pelvic exenteration. The early cases subjected to this operation were unselected. Many of these patients were in such poor physical condition that they could not survive the operative shock. In others, the tumor had either spread beyond the pelvis or had invaded the pelvic fascia or bone so that tumor was transected in removing the major lesion. Brunschwig and Daniel[13] later noted that when gross tumor was left behind, the average survival of these patients was slightly over 3 months. When it became apparent that by proper selection of cases certain patients would survive pelvic exenteration and live happy and useful lives thereafter, the emphasis shifted from palliation to an attempt to produce a cure. Parsons and Taymor[22] have written that the survival of a patient for 2 years following exenteration justifies the performance of this type of surgery. Therefore in evaluating patients for pelvic exenteration, any obvious spread of the tumor to the lungs, bones, or other distant organs is a contraindication to operation. In some instances, very early distant metastasis cannot be detected preoperatively. Leg edema and parametrial fixation have come to be regarded as ominous signs. Bricker *et al.*[3,6] do not consider sciatic pain and hydronephrosis to be reliable signs of inoperability. Most authors agree that often only an exploratory laparotomy will permit a definite decision. Involvement of the liver or spread to para-aortic nodes precludes further operation. If the question of operability concerns local fixation of the tumor in the pelvis, at operation a considerable amount of pelvic dissection can be done, especially along the lateral pelvic wall, before the surgeon finds himself committed to complete the operation.

When it is apparent that such surgery is indicated, a preoperative emotional evaluation is in order. A review of all of the facts should be presented to the patient and a responsible member of her family. At times there will be immediate refusal to submit to this type of surgery. The patient may then return at a later date in much less favorable condition for operation, or she may be even found inoperable. If the surgeon is associated with the indi-

viduals who have given the primary therapy, his rapport with the patient will usually be much better, and she is more likely to heed his advice. It is quite important to explain the risk involved, the financial and economic problems which are likely to occur, the necessity for abdominal stomas for the excretion of urine and feces, and any other problems in which she or her family express an interest. It is often wise to seek the consultation of a psychiatrist to determine the ability of the patient to tolerate the emotional trauma associated with this type of surgery.

The preoperative evaluation must be thorough, for the patient's physical condition should be as optimal as possible. The routine study should include the following: hemoglobin, hematocrit, red and white blood counts, urinalysis, fasting blood sugar, blood urea nitrogen, carbon dioxide combining power, chloride, potassium, sodium, total serum protein, serum albumin and globulin, alkaline phosphatase, blood coagulogram, blood volume, electrocardiogram and intravenous urogram. The extent of local and distant involvement is determined by means of cystoscopy, proctoscopy, barium enema, chest film and bone survey. Medical and anesthetic consultations should also be requested.

After the patient's total physical and emotional status are critically evaluated, if these are regarded as satisfactory, preparation for surgery is begun. Any blood volume deficit must be replaced. Vigorous efforts are made to eradicate infection from the urinary tract and from the vagina. This is accomplished through the use of appropriate local and systemic antibiotic and chemotherapeutic agents. The intestinal tract is prepared by means of antibiotics, purgatives and enemas. Preoperative decompression of the small bowel is accomplished by the use of the Miller-Abbott tube.

There is some controversy regarding the extent of surgery to be performed. Bricker and Modlin[6] are of the opinion that when secondary treatment of cervical cancer by pelvic exenteration is contemplated, the total exenteration should always be done. This point of view is based on the fact that it is usually impossible to determine the extent of tumor involvement by clinical means. Schmitz and Gajewski[23] raised this question, "Is it not conceivable that as our experience increases, we shall sacrifice the bladder and rectum more often, as this expedites the removal of the diseased tissues and gives greater assurance that we have the diseased areas most likely to be involved, bladder, rectum, ureters and regional nodes, removed?" Brunschwig and Daniel[14] do not agree with these authors. They state, "Surgery is not unduly extended in a prophylactic sense, *i.e.*, the fact that a lesion localized to the cervix or upper vagina has not been controlled by radiation does not call for a total pelvic exenteration because of the impression that since radiation therapy has failed and time has elapsed, the disease 'probably' has spread to adjacent viscera." There is much to be said for each viewpoint. A lesser operation is attended with a lower mortality. However, when we consider exenteration in its present light as an all-out effort at cure, the stand for total exenteration becomes logical. The survival statistics relating to partial and total exenteration, with similar clinical degrees of involvement, should provide the answer in the future.

During the operation, the patient must be under the scrupulous observation of a competent anesthetist, and the choice of anesthesia is left to his judgment. Sudden or prolonged hypo-

tension, hypoxia, and inadequate blood replacement must be avoided. The blood loss is measured as accurately as possible so that replacement can be instituted promptly. Since the majority of patients have had previous irradiation, the dissection is usually more difficult and more bloody due to the loss of the normal cleavage planes. Under these circumstances, hemostasis is more readily obtained by means of pressure or packing, than by clamping and ligation. Some authors[22,25] agree that pelvic exenteration can be completely done through the abdominal approach, thus avoiding a perineal phase. This maneuver is less shocking to the patient and also saves valuable time.

During the immediate postoperative period, strict attention is given to the problems of shock, hemorrhage and infection. Adequate preoperative preparation pays great dividends in reducing the incidence of these complications. Antibiotics, blood, plasma, and proper fluid and electrolyte replacement are of vital importance. The maintenance of adequate pulmonary ventilation and blood circulation is aided by turning the patient, and encouraging her to move herself and to breathe deeply. Bricker *et al.*[3] reported 15 instances of intestinal obstruction in 118 patients who had total pelvic exenteration. This is a rather significant complication, and it can be most troublesome since the usual signs associated with this problem may not be overtly manifest. The late postoperative phase is directed toward teaching the patient to live with her altered anatomy, and with the maintenance of both her nutrition and her morale. She must always be encouraged to live an essentially normal life.

Significant among potential complications associated with pelvic exenteration are those dealing with the urinary tract. Diversion of the urinary stream associated with removal of the urinary bladder creates one of the major physiologic problems. The preoperative presence of renal impairment adds to the hazard of the procedure, and may be the chief reason for an unsuccessful result.

Brunschwig and Daniel[12,14,15] have used cutaneous ureterostomy and ureterosigmoidostomy, either as a wet colostomy or by implantation of the ureters into the sigmoid colon above an intact anal sphincter. A long-term follow-up on 10 patients whose urine was diverted by these methods, and who were still living from 4 to 7½ years after operation, revealed considerable difficulty with urinary stasis and electrolyte imbalance. This was especially true in the patients whose urinary stream was diverted to the colon above an intact anal sphincter. Parsons and Taymor[22] used similar forms of urinary diversion and reported recurrent episodes of pyelonephritis in 9 of 16 patients living from 2 to 6½ years after operation. Recently they have employed a transverse colostomy proximal to the ureterosigmoidostomy to free the left colon from the flow of feces. This apparently decreases the incidence of renal infection. Douglas and Sweeney[18], who also used these forms of urinary diversion, reported that among 23 pelvic exenterations, 20 patients had postoperative hydronephrosis and 18 suffered from pyelonephritis.

In 1950, Bricker[2] introduced an operative technique utilizing the principle of isolated bowel conduits. The chief purposes of the isolated segment operation are to prevent infection, decrease urinary stasis, and to avoid the need for indwelling tubes. Bricker *et al.*[3] performed 118 total exenterations and implanted the ureters into an isolated segment of terminal ileum in all but 2 of these patients. There were 15 postoperative deaths in this group, and 5

were found to be related to the urinary diversion part of the operation. It is noteworthy, however, that of 55 complications among 34 patients, only 8 were associated with the urinary tract. In addition, there was only one instance of pyelonephritis among the complications. In the late postoperative period, 2 deaths were attributed to urinary tract complications. Wawro and Howe[26] have also reported satisfactory results with ureteroileostomy in 44 exenteration operations.

There is some disagreement at present whether the isolated bowel procedure should be added to an already shocking operation. In 1955, Brunschwig and Daniel[15] wrote, "until evidence is produced to the contrary, we will continue to regard the formation of the wet colostomy as the method of choice for diversion of both urinary and fecal drainage following total pelvic exenteration." The accumulation of satisfactory results following pelvic exenteration that is combined with urinary diversion to an isolated segment of bowel, strongly suggests that such a procedure deserves serious consideration. The removal of the long-term insult to the kidneys by the use of isolated bowel conduits allows pelvic exenteration itself to be more honestly evaluated as a means of management of pelvic cancer.

**Summary.** The employment of pelvic exenteration in the management of pelvic malignancy has been sufficiently evaluated so that it is no longer considered a surgical experiment. The results that have been published indicate that immediate and long-term survival are possible. There is also increasing evidence to show that carcinoma of the uterine cervix is the most suitable lesion for treatment by pelvic exenteration. It should be understood that this operation is not meant to supplant the primary radiation treatment which has proved so successful in the control of cervical cancer. Rather, it should be reserved for certain instances of recurrent tumors following radiation, radioresistant tumors, occasional Stage IV lesions, and severe radiation necrosis.

Selection of patients for pelvic exenteration should have as its aim the prospect of a cure. This is accomplished through extensive preoperative study to rule out distant metastasis, and even laparotomy, if needed, for a final decision. The performance of pelvic exenteration for palliation does not appear to be warranted.

At present, two of the most significant problems concerning pelvic exenteration for cervical cancer are the extent of the operation, and diversion of the urinary stream. The all-out approach by total exenteration versus partial exenteration needs further evaluation and study. The risk of leaving residual tumor must be weighed against the higher mortality of the total operation. Likewise, the use of an isolated intestinal segment for urinary diversion, while reducing the chronic renal problem, prolongs an already lengthy procedure. With any other type of urinary diversion, successful eradication of the tumor may be nullified by serious complications and even death from chronic urinary tract infection, stasis or electrolyte imbalance.

Until more information is acquired concerning the nature of malignant disease, and less drastic and more successful means of cure have been discovered, pelvic exenteration will remain as a valuable part of our armamentarium in the management of cervical cancer.

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# BOOK REVIEWS AND NOTICES

TUBERCULOSIS IN WHITE AND NEGRO CHILDREN. VOLUME I. THE ROENTGENOLOGIC ASPECTS OF THE HARRIET LANE STUDY. BY JANET B. HARDY, M.D.C.M., Johns Hopkins University. Pp. 122; 246 ills. Cambridge, Mass.: Harvard University Press, 1958. Price, $7.50.

TUBERCULOSIS IN WHITE AND NEGRO CHILDREN. VOLUME II. THE EPIDEMIOLOGIC ASPECTS OF THE HARRIET LANE STUDY. BY MIRIAM E. BRAILEY, M.D., DR.P.H., Johns Hopkins University. Pp. 103. Cambridge, Mass: Harvard University Press, 1958. Price, $4.50.

IN 1928 a special outpatient clinic was established at the Johns Hopkins Hospital to study tuberculosis in children. Children under 2 years of age who were already infected with tuberculosis, or were members of households containing one or more sputum-positive adults, were admitted to the clinic. Siblings under the age of 15 with demonstrable infections were also included in the study. In all, 437 white children and 892 Negro children were followed. The outstanding feature of the study is that follow-up continued until 1950, a maximum of 22 years. This falls short of the "ideal" study, which would follow every tuberculin-converter for life, but represents a much longer and more meticulous observation than can be found in most comparable American reports. Only the Scandinavians have essayed similar long-term projects. Four percent of white children and 2.3% of Negro children were lost to follow-up. This was largely due to the fact that the same skilled worker directed the social service aspects of the study for 22 years.

Volume I contains the highlights of the roentgenologic aspects of the study. All types of primary pulmonary infection are illustrated, as are well selected examples of extrapulmonary tuberculosis, reinfection tuberculosis, and nontuberculous conditions giving rise to questions of differential diagnosis. The illustrations are intelligently selected and admirably reproduced in large size on glossy paper. The captions are brief and easily understood. A valuable section, written in collaboration with Dr. Donald F. Proctor, describes the special techniques of bronchoscopy and bronchography in children.

Volume II discusses the epidemiologic aspects of the study. .Data were subjected to life-table actuarial methods, so that the reader may learn, not only the actual number of children who developed certain complications or died, but the expected rate per 1000 per year of observation. Many pertinent facts were statistically established, including the preponderance of mortality in the first year of known infection; the greater seriousness of first infection in Negro children, the risk of developing reinfection tuberculosis being ten times as high in Negro children as in white children. Interesting statistics are presented concerning the subsequent course of children in whose homes contact with a sputum-positive adult was broken, and those with contact maintained. It seemed to make little difference with white children, but tripled the percentage of Negro children who developed reinfection tuberculosis within 10 years.

Since this most valuable study covers the period just before the present age of antibiotic and chemotherapeutic attack on tuberculosis, one might ask, is it still pertinent? The reviewer feels that it most certainly is, perhaps more so than ever before. The radiologist, clinician and pediatrician will continue to see radiographs like those illustrated in Section I, but these will soon become relative rarities instead of commonplace, well known conditions. Those entrusted with the treatment of children infected with tuberculosis, with or without radiographic evidence of disease, should know which child *must* be treated, which *may* be treated, and which (if any) may safely be left alone. Enthusiasts for the mass treatment of all tuberculin converters should know what to expect of untreated converters. Finally, in too many parts of the world today, the tuberculosis control situation is still far worse than it was in the slums of Baltimore during the depressed 1920's and 1930's. The results of the Harriet Lane Study should encourage public health workers to attack tuberculosis vigorously, at all times, and in all places.

R. C.

---

DIETARY PREVENTION AND TREATMENT OF HEART DISEASE. BY JOHN W. GOFMAN, PH.D., M.D., ALEX V. NICHOLS, PH.D., AND E. VIRGINIA DOBBIN, Senior Dietitian, University of California. Pp. 256; 4 ills. New

York: G. P. Putnam's Sons, 1958. Price, $3.95.

THE prevention of heart attacks by diet is the principal theme of this book. Its purpose is to instruct in the selection and implementation of the proper diet. It is maintained that the risk of heart attacks is high when blood lipoproteins in the Sf 0–12, 12–20, 20–100 and 100–400 classes are high and that the risk can be lowered by their decrease. Essentially, the diet is low in animal fat if the Sf 0–12 and 12–20 classes are elevated, and low in carbohydrate if the Sf 20–100 and 100–400 classes are elevated. Saturated vegetable fats behave like animal fat. On the other hand, unsaturated vegetable fats are recommended only to increase satiety and palatability and have no other beneficial effect. The diet is not primarily concerned with indiscriminate reduction of calories. Selection and preparation of diets are carefully described and many recipes are given. Finally, foods are listed with their content of high and low saturated fats, protein and carbohydrate.

Diet is indicated only in those with an elevation of one or all of the specific lipoproteins and its kind depends upon the lipoprotein findings. For these reasons, it is necessary for all to have a prior blood analysis for determination of type and amount of lipoproteins. The results of such an analysis would make suspect, according to the cooperative study group of the American Heart Association, about one-half of the male population for whom Gofman would recommend special diet. Yet, it has not been established that specific lipoprotein findings have predictive value and that diet has prophylactic value.

The protagonists will be delighted with this book, the antagonists will scoff and the "neutralists" will enjoy the battle, perhaps while eating less meat and chicken, more fish and vegetables, little bread and no butter, and appeasing their hunger by more nuts and caramels. Finally, the gourmet, that staunch defender of Epicureanism, will remind all of them that when, in the history of medicine, knowledge was incomplete, the approach to disease was dietary. J. Z.

---

THE MEASUREMENT AND APPRAISAL OF ADULT INTELLIGENCE. By DAVID WECHSLER, Chief Psychologist, Bellevue Psychiatric Hospital, Adjunct Professor of Psychology, Graduate School of Arts and Science, New York University. 4th ed. Pp. 297. Baltimore: The Williams & Wilkins Company, 1958. Price, $5.00.

THIS book is a distillation of the author's thinking about intelligence and the ways of measuring it, a field which has been his main endeavor since 1939 when the Wechsler-Bellevue Intelligence Scale first appeared and followed more recently by the Wechsler-Adult Intelligence Scale. These are the most widely used tests for a comprehensive evaluation of adult general intelligence in the United States today. Dr. Wechsler's book serves as background both for his theoretical concepts of intelligence and their translation into an operational, quantitative, testing procedure.

Part I deals with the nature, classification, and appraisal of intelligence. Part II deals with a technical description of the composition of the W.B. and the W.A.I.S., as well as the standardization procedures and studies that went into the effort to make the tests representative. Part III is concerned with diagnostic and practical applications which, along with Part I, is more relevant for the physician.

Dr. Wechsler believes that any practical definition of intelligence must be fundamentally a biological one, and disclaims any identification of general intelligence with sheer intellectual ability. Learning, adapting, reasoning, and other forms of goal-directed behavior are only different ways in which intelligence (itself an abstract construct) is manifested. The essential justification of an intelligence test is that it can harness these various abilities in a standardized situation to arrive at a global estimate of intelligence.

Dr. Wechsler operationally defines intelligence as "the aggregate or global capacity of the individual to act purposefully, to think rationally, and to deal effectively with his environment." One of the gratifying aspects of this book is his emphasis on the nonintellective components which enter into intelligent behavior; namely, the interaction of intelligence, with affective and emotional components of the personality, so that intellectual functioning is viewed as dynamic. For the physician who wants familiarity with this area of psychological thought, this book is recommended. M. B.

---

SELECTED WRITINGS OF JOHN HUGHLINGS JACKSON. VOL. 1: ON EPILEPSY AND EPILEPTIFORM CONVULSIONS. VOL. 2: EVOLUTION AND DISSOLUTION OF THE NERVOUS SYSTEM, SPEECHES, VARIOUS PAPERS, ADDRESSES AND LECTURES. Edited by JAMES

TAYLOR, M.D. Pp. 500 and 510; 2 ills. New York: Basic Books, Inc., 1958. Price, $15.00 the set.

THIS is the first American edition of the two volumes of writings of John Hughlings Jackson. The English edition was published in 1931, and the appearance now of an American edition is both welcome and needed. The two volumes deal with Jackson's many original contributions. The first volume is confined to a discussion of epilepsy and epileptiform convulsions and contains Hughlings Jackson's most important contributions to a field which he enriched by original thinking. In his original articles can be found the basis for much of our present-day orientation in the entire field of epilepsy.

The second volume contains Hughlings Jackson's famous discussions on Evolution and Dissolution of the Venous System and his significant contributions to the problem of aphasia, a subject which was as congenial to him as the problem of epilepsy. The remainder of the volume contains addresses, papers and lectures on many subjects including his Hughling Jackson lecture on the levels in the venous system and their relationship to one another. The miscellaneous subjects which received his attention covered a wide range of subjects: chorea, vertigo, optic neuritis, brain tumors, cerebellum, and many other pertinent problems.

The material contained in these papers is of historical interest, but it has an importance far beyond this, for it constitutes required reading and re-reading for all those interested in the nervous system. B. A.

---

PHARMACOTHERAPIA. BY DR. MED. GEORGE ARNAUDOV, Sofia, Bulgaria. 3rd ed. Pp. 1028. Sofia, Bulgaria, 1957.

THIS rather extensive yet condensed book on pharmacopoeia and therapeutics summarizes essentially the same ideas that are well known in this country. They include the old drugs as well as the new ones. They do not contain anything especially important that has developed in the Russian and satellite areas. The only new antibiotics described are: Ecmolinum, developed in the USSR, which has certain antihistaminic reactions. It is supposed to be most effective against typhus and dysentery bacteria such as the cholera, colon bacillus and also the virus of grippe. It is also supposed to enhance the action of penicillin and streptomycin. Another antibiotic is Synthomycinum which resembles chloromycetin in its action on dysentery and typhus organisms. Then there is Albomycinum, which was developed in Russia; it is active against Gram-positive and Gram-negative bacteria including staphylococcus, pneumococcus and colon organisms. It is supposed to be more effective than penicillin in children less than one year of age. Except for this, there is nothing especially new.

The book is fairly well written and is intended for students as well as practicing physicians, who can read Russian. The author is a well known clinician and therapeutist. G. B.

---

THE PSYCHIATRIC HOSPITAL AS A SMALL SOCIETY. BY WILLIAM CAUDILL, Harvard University. Pp. 376; 11 ills. Cambridge: Harvard University Press, 1958. Price, $6.50.

OVER a several month period the author was an observer in a small psychiatric hospital. This book presents the results of his inquiry into the nature and influence of the social structure of the hospital on both the personnel and patients. Most striking is the demonstration of the influence that patients have on one another to which the therapist, in his focus on the patient alone, often remains blind. It is the author's contention that an understanding of the social milieu to which patients are daily exposed is imperative to therapy in a hospital setting.

Three principal methods of study were employed: 1) Direct observation of life on the wards; 2) a picture-interview analogous to the TAT administered to staff and patients specially designed to elicit attitudes toward hospital life; and 3) analysis of the interaction at daily administrative conferences.

As a social anthropologist with previous experience at Yale studying the interplay between social factors and mental illness, the author is particularly well qualified for his task. M. B..

---

ADVANCES IN ELECTROCARDIOGRAPHY. Edited by CHARLES E. KOSSMANN, B.S., M.D., MED.SC.D., F.A.C.P., Associate Professor of Medicine, New York University College of Medicine; Visiting Physician, Bellevue Hospital. Pp. 280; 134 ills. New York and London: Grune & Stratton, Inc., 1958. Price, $9.75.

THIS book is based upon a course in electrocardiography sponsored by the American College of Physicians at the New York University Bellevue Medical Center under the direction of the Editor. The course was restricted to recent advances in electrocardiog-

raphy which were considered to be of greatest immediate or future significance. The Editor, well known for his own contributions of a fundamental nature to the field of electrocardiography, has accomplished his task with distinction. This book is recommended to those who have mastered conventional electrocardiographic texts and also as a review for those familiar with most of the advances.

The book is divided into five parts, 1) source of potential; bioelectrics of the myocardial cell; 2) conducting medium; electric field of heart; leads; 3) spread of excitation and recovery, normal and abnormal; 4) rhythms; and 5) summary and conclusions.

The reader should remember that there is no royal road to knowledge. Certain subjects (for example, electric field) may be unintelligible in synopsis form. He should be inspired to turn to the original sources.

The reviewer was disappointed that Kossmann's conclusions were not more critical and particularly because he did not compare his colleague Shultz's work with Bryant's disproportionately long chapter.

The American College of Physicians is to be congratulated for having the foresight to sponsor a course like this by Kossmann.

L. S.

---

INTERMEDIATE HOSTS OF SCHISTOSOMA. African *Biomephalaria* and *Bulimus*. Monograph Series No. 37. By G. MANDAHL-BARTH. Pp. 132; 60 ills. Geneva: World Health Organization, 1958. Price, $4.00.

THIS excellent monograph is the first comprehensive study concerned with the species identification of snails belonging to the genera *Biomphalaria* and *Bulimus* that serve as intermediate hosts in the spread of bilharziasis in Africa. In attempting to classify the various species of these genera 5500 specimens from 794 different populations were studied.

Experts in the field of malacology should welcome this attempt by the author to classify the various species of these genera. This excellent study should serve as a basis for more advanced work in relation to these snails of medical importance in Africa.

E. G.
A. L.

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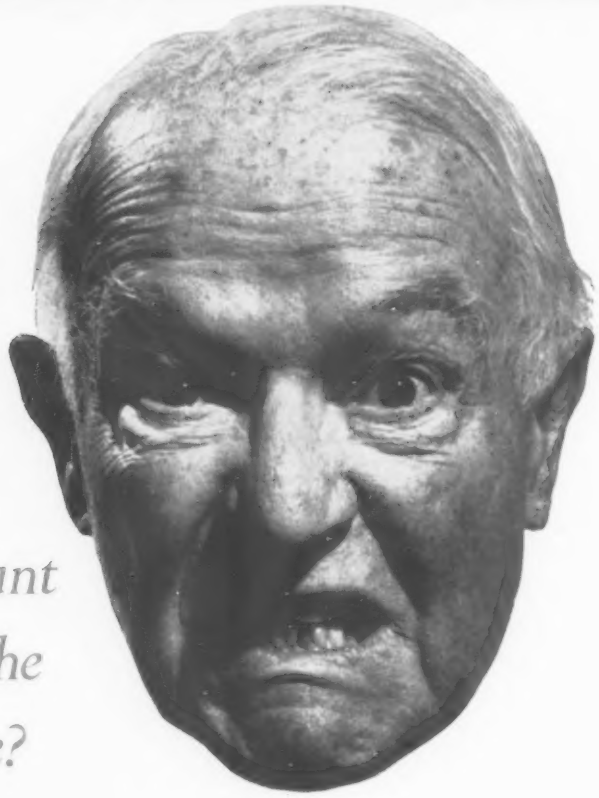

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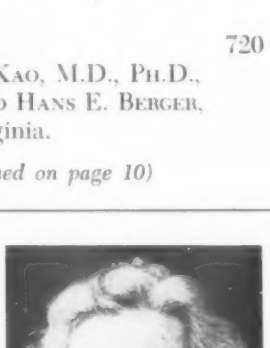

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**COMMUNICABLE DISEASES**

*A Bibliography of Internal Medicine*

*by* ARTHUR L. BLOOMFIELD, M.D.

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*(Contents continued on page 14)*

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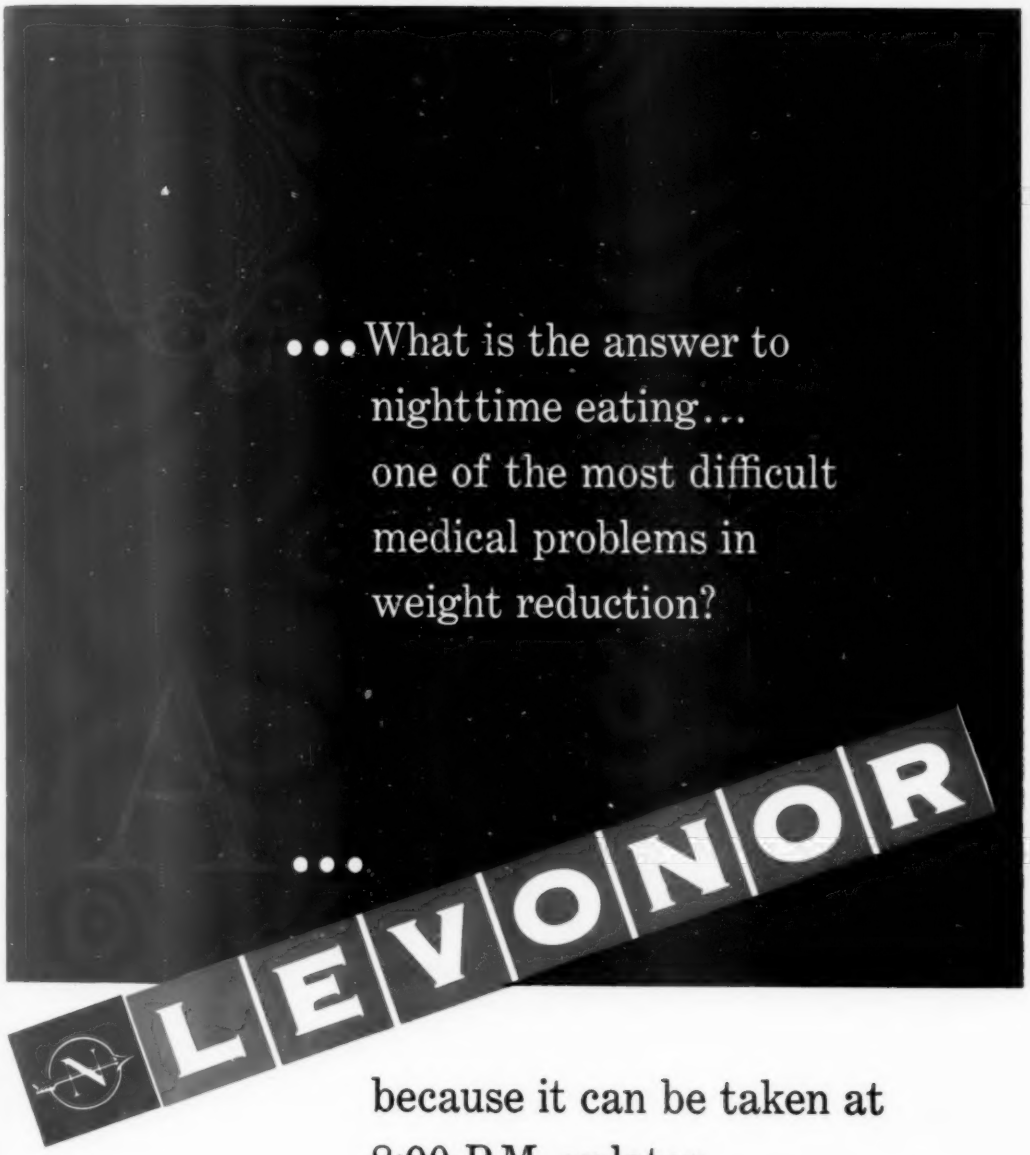


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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955.

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*Biegeleisen, H. I.; Clinical Medicine; Oct., 1955

*Roberts, J. T.; Clinical Medicine; Nov., 1957

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

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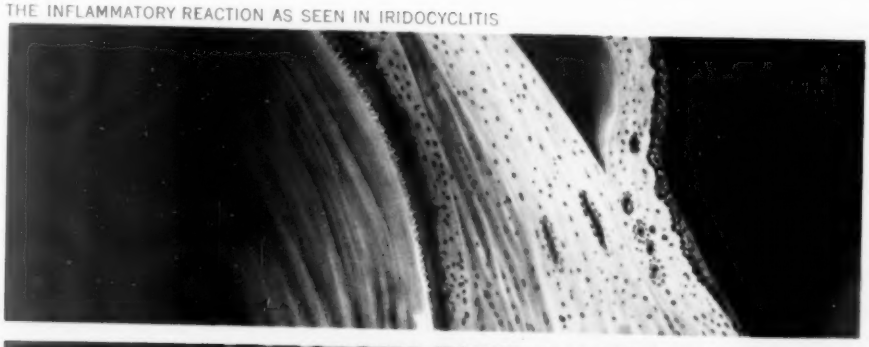
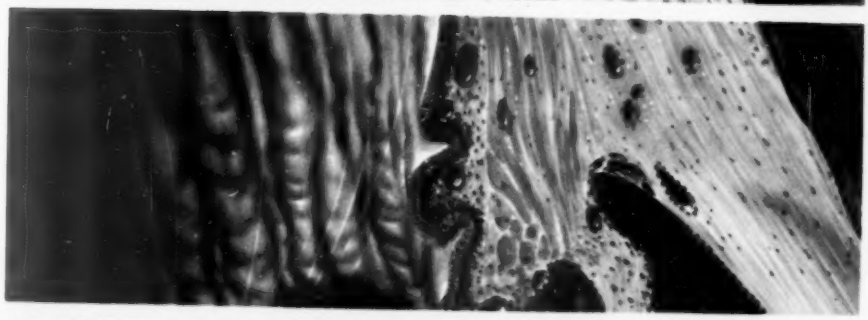
EXUDATIVE INFLAMMATION OF THE UVEAL TRACT

THE INFLAMMATORY REACTION AS SEEN IN IRIDOCYCLITIS

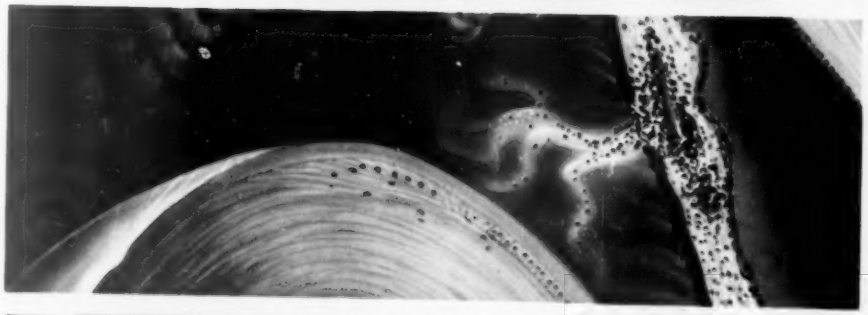
**A.** Normal tissue. From left to right: posterior surface of ciliary ring, ciliary retina, pigmented layer, ciliary muscle, sclera, and conjunctiva.



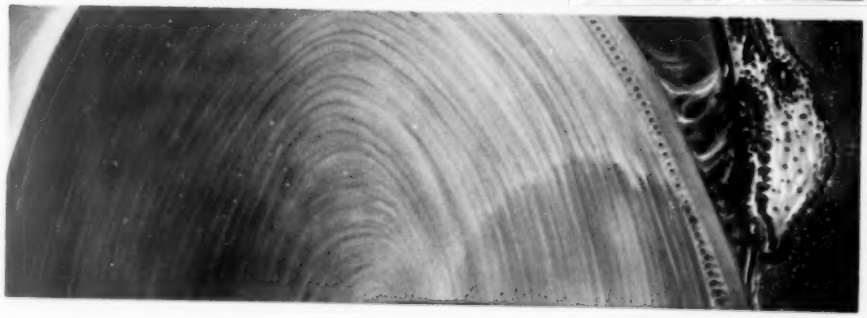
**B.** Hyperemia is the result of reaction to an endogenous toxin or allergen. Blood vessels are dilated. There is heightened local heat and color. Escape of blood plasma causes edema.



**C.** The next stage is that of exudation, shown here as macrophages and fibrin streaming from the posterior surface of the iris.



**D.** As the condition becomes subacute, there is concomitant active exudation and repair. With chronicity, fibroblasts proliferate, new capillaries develop, and various kinds of white cells appear. Formation of a posterior synechia is shown.



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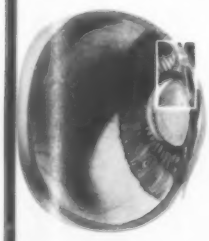


IN OCULAR INFLAMMATORY DISEASES Medrol

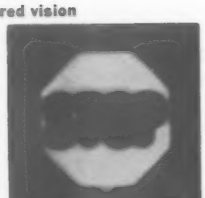
A SYNOPSIS OF OCULAR INFLAMMATORY DISEASE (IRIDOCYCLITIS)

Subjective symptoms:

**Photophobia**

**Trigeminal pain**

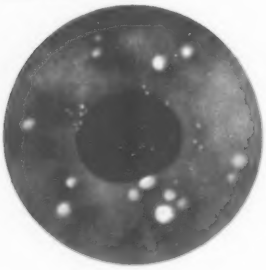
**Blurred vision**



**Lacrimation**

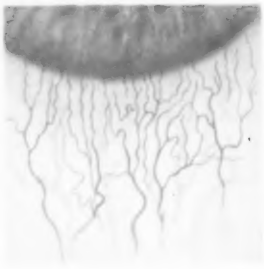
Clinical findings:

**Hazy iris**



**Swollen upper lid**

**Ciliary injection**



Sequelae: (if untreated)

**Anterior and posterior synechiae**

**Lenticular changes**

**Secondary glaucoma**

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Medrol now makes it possible for you to choose *systemic* corticotherapy as first treatment in many eye disorders. You gain the greater efficiency that systemic corticotherapy gives, yet take almost as little risk as with topical applications, because Medrol is so outstandingly free from most corticosteroid side effects. In fact, it can reverse the sodium and water retention caused by older steroids.[1]

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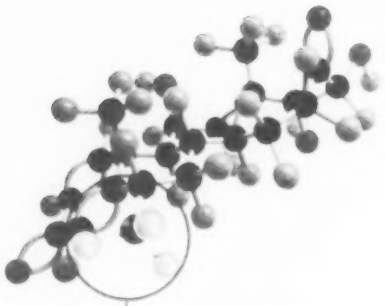

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- good results with Medrol with no deleterious reactions

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- striking clinical improvement in patients with chronic lymphocytic leukemia

**IN OPHTHALMIC DISORDERS**
the molecular difference of Medrol results in
- superior effectiveness and safety in ocular allergies, acute and chronic uveitis, and other disorders of the posterior segment

**IN ALLERGIC DISORDERS**
this corticoid effectiveness of Medrol leads to
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- lowest incidence of side effects on record (about 4%)

**IN DERMATOSES**
Medrol's distinctive formula achieves
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- markedly shortened treatment period
- drastic reduction in incidence and severity of side effects

**IN RHEUMATOID ARTHRITIS**
Medrol's chemical distinction is reflected in
- good to excellent results in nearly all cases
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- fewer and milder side effects than with any other corticoid

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1. Feinberg, S. E.: Medrol in Allergic Conditions: Clinical and Experimental Findings, Metabolism 7:477 (July) 1958.
2. Gordon, D. M.: Methylprednisolone in Ophthalmology, Metabolism 7:569 (July) 1958.

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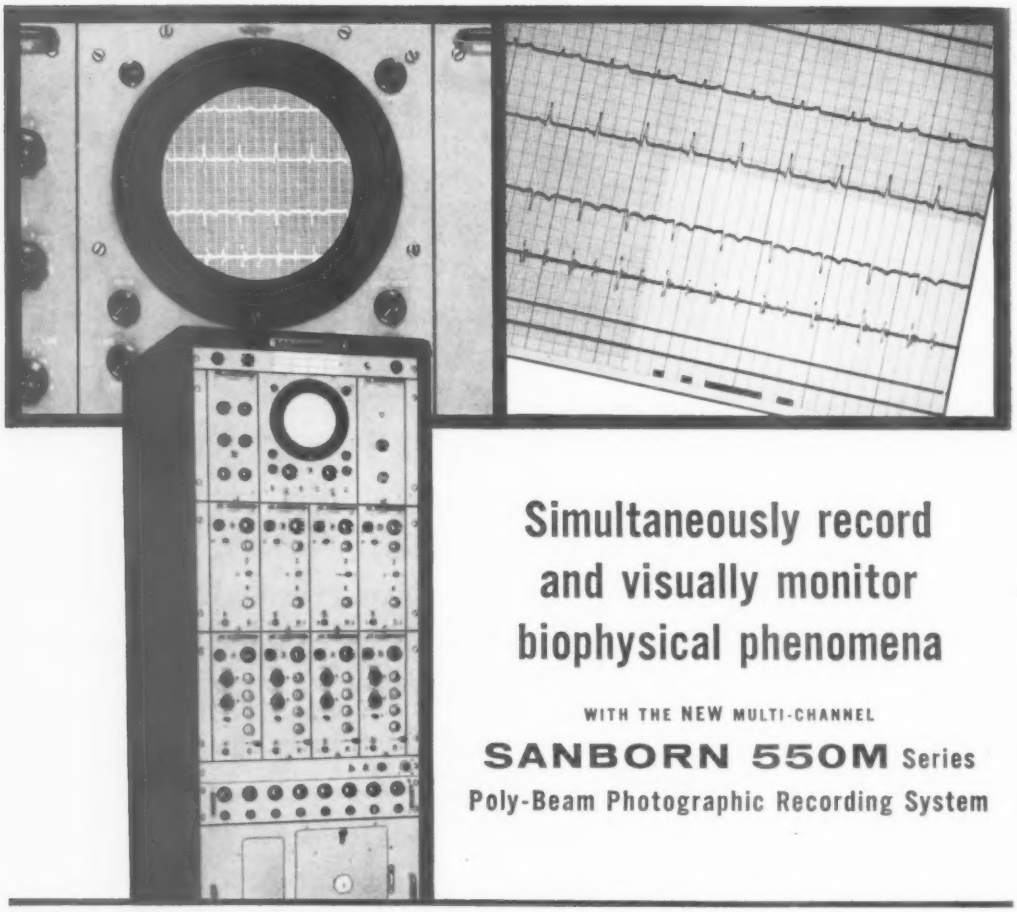

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1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.
2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

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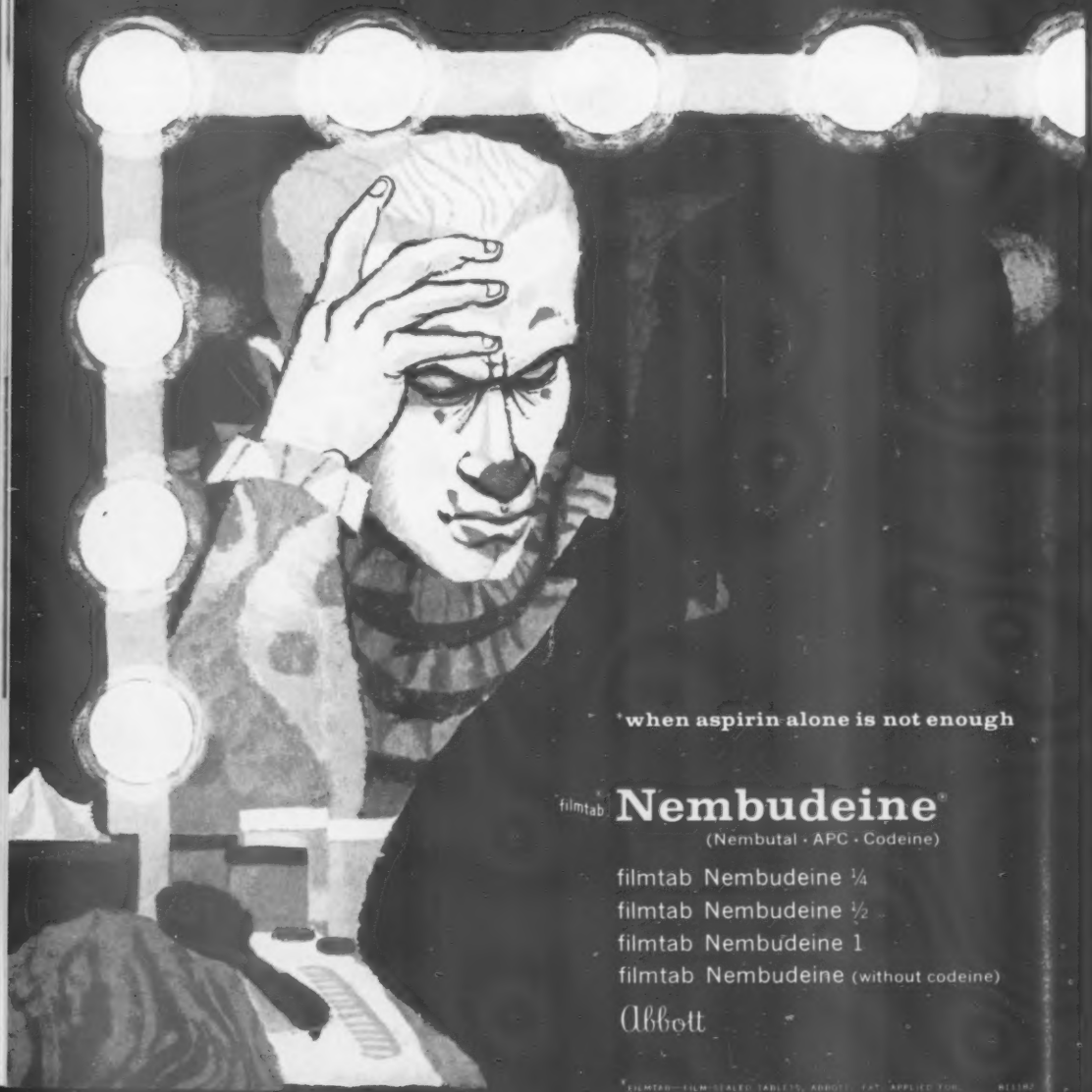

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SUMMIT, N. J.

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# Exactly how does new Halodrin* restore the "premenopausal prime" in postmenopausal women?

Webster defines "prime" as the period of greatest health, strength, and beauty. In a woman, these are the childbearing years between puberty and menopause—the years when her hormone production is highest.

The inevitable reduction in this hormone production as she enters the menopause often results in physical discomfort in the form of hot flushes, nervousness, insomnia, or a multiplicity of other symptoms with which you are familiar. Superimposed on this physical picture is the psychic trauma brought on by this unavoidable evidence of aging. The thing that brings her to a physician is simply that she "feels bad."

You can't make her 35 again—but the odds are good that you can make her **feel** like it! The secret is a combination of reassurance and hormones. The exact form and amount of the former defy objective analysis, but the latter can now be provided with scientific precision. Reduced to essentials, here is the explanation of exactly how hormones—in the form of Upjohn's new Halodrin—restore the "premenopausal prime."

The normal premenopausal woman excretes estrogens in the urine in the form of estradiol, estrone, and estriol, in an approximate 28-day average ratio of 39:15:46. Starting with this urinary excretion of estrogens, it is possible to calculate backwards and estimate the amount of estradiol that must have been secreted endogenously in order to produce these urinary levels. This is possible because the proportion of estrogens which appears in the urine following parenteral administration has been established in castrated women.

On this basis, the average endogenous output of estrogens is about 160 micrograms per day during a menstrual cycle, and 80 micrograms per day in postmenopausal women (see chart opposite). Therefore, the restoration of the "premenopausal prime" in the postmenopausal woman requires the replacement of approximately the equivalent of the 80 micrograms of estradiol per day that she no longer secretes endogenously.

**Oral** ethinyl estradiol is about 2 to 2½ times as potent as **parenteral** estradiol. Therefore, **the replacement of 80 micrograms of endogenous estradiol production per day is accomplished by the oral administration of 32 to 40 micrograms of ethinyl estradiol per day.**

Each Halodrin tablet contains 20 micrograms of ethinyl estradiol, which means that the recommended dosage of 2 tablets per day provides 40 micrograms of ethinyl estradiol. This offsets the loss of 80 micrograms of endogenous estradiol production in the menopausal woman; i.e., restores the "premenopausal prime."

Each Halodrin tablet also contains 1 mg. of Upjohn-developed Halotestin* (fluoxymesterone)—the most potent oral androgen known. The primary purpose is to "buffer" the ethinyl estradiol just enough to prevent breakthrough bleeding, which is obviously undesirable in the menopause. It also exerts other beneficial hormonal effects, one of which, in common with ethinyl estradiol, is a powerful anabolic action so desirable in patients of advanced years.

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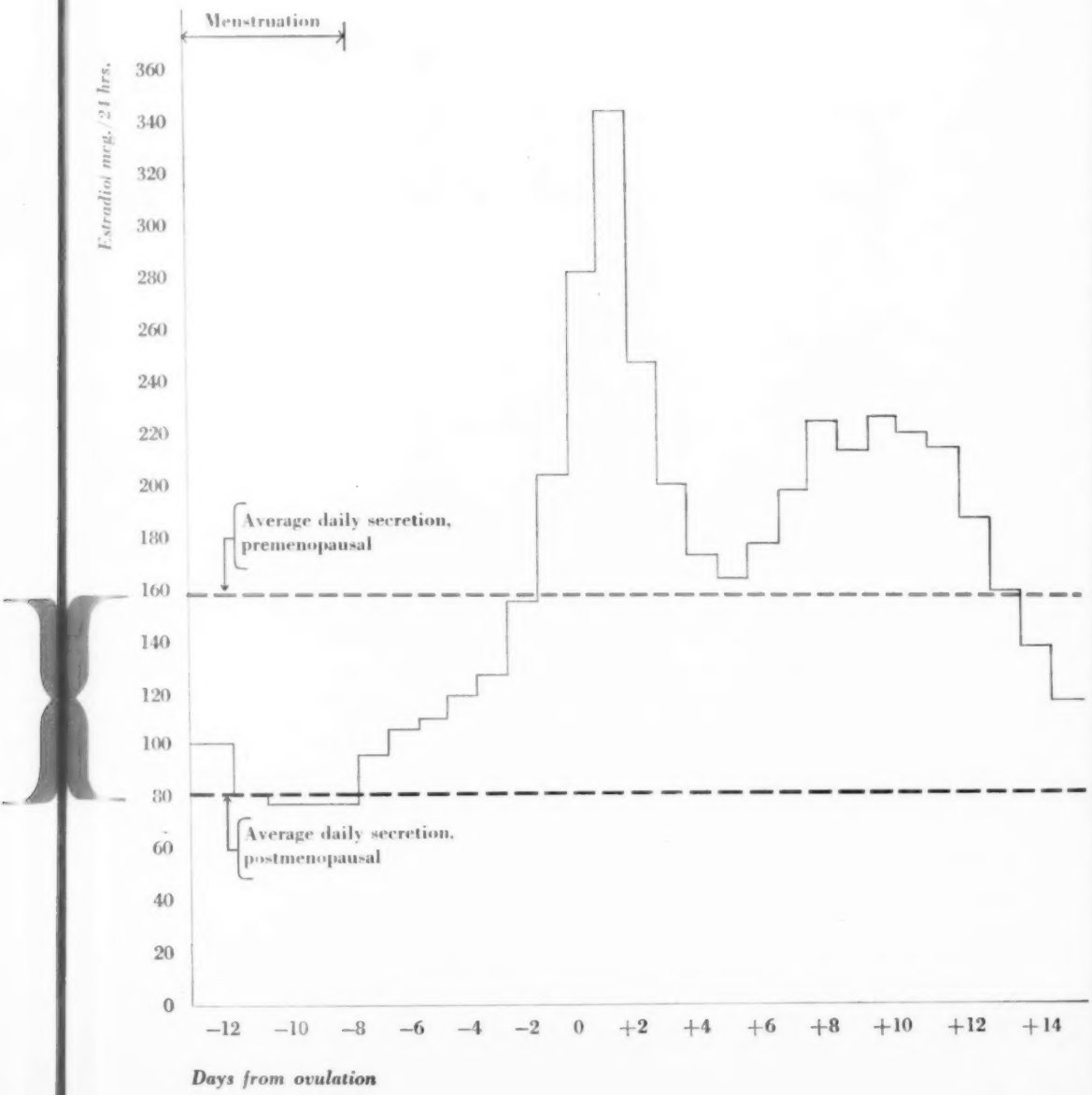
**Endogenous estrogen secretion (mcg./24 hours)**
**(calculated from average 24-hour urinary excretion of estradiol, estrone, and estriol)**



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BECKER, M. C., Simon, F. and Bernstein, A.: J. Newark Beth Israel Hosp. **9**:58 (January) 1958.

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250 mg., 125 mg.
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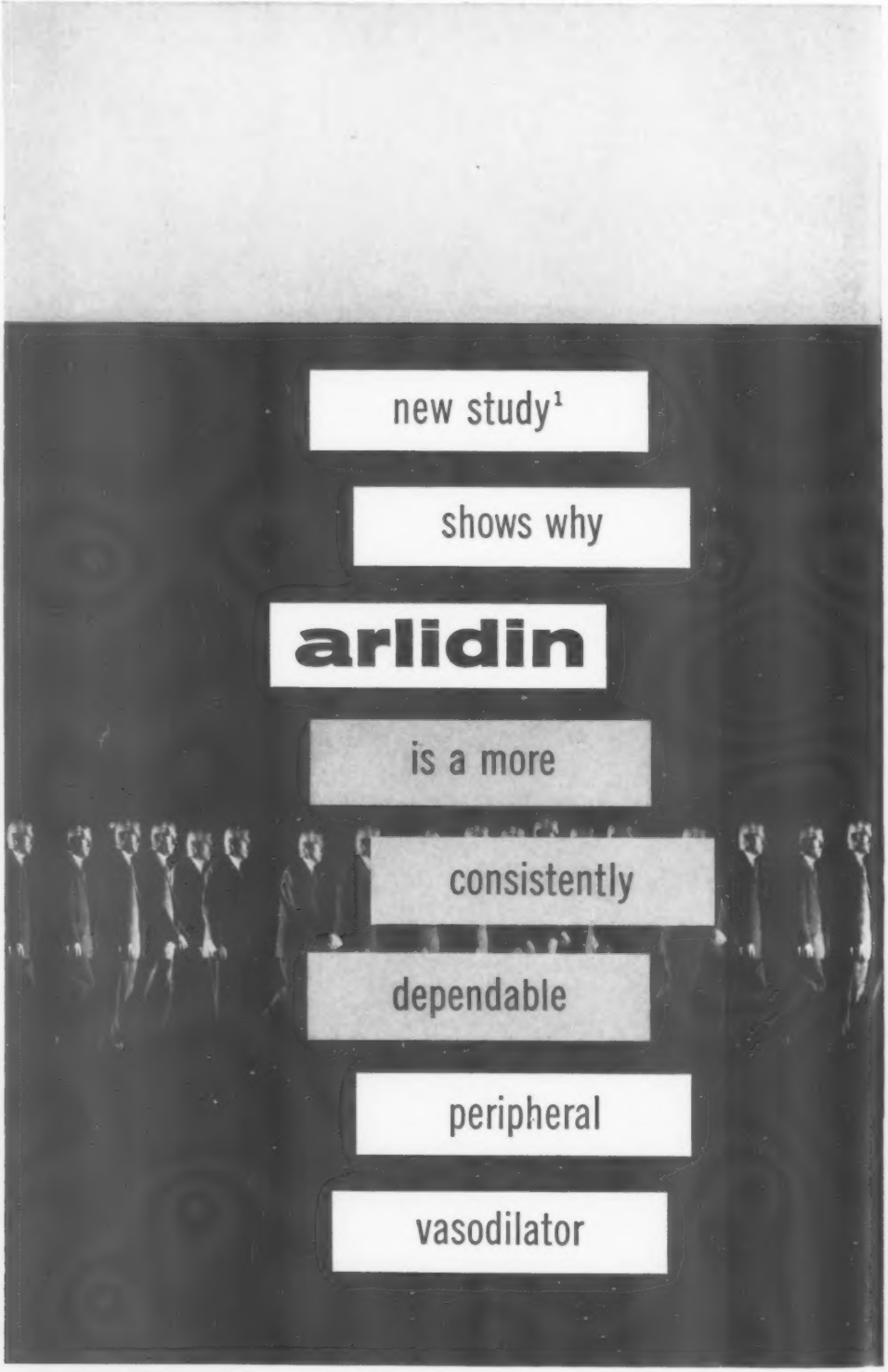
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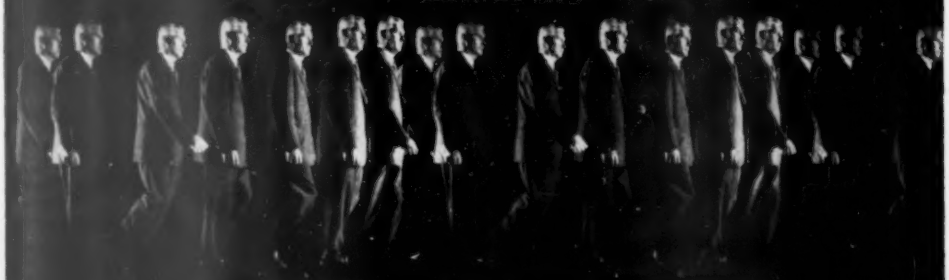

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See PDR for dosage and package sizes

1. Murphy, H. L., and Klasson, D. H.: New York St. J. M. 57:1908, June 1, 1957

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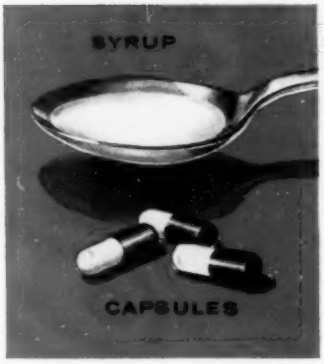


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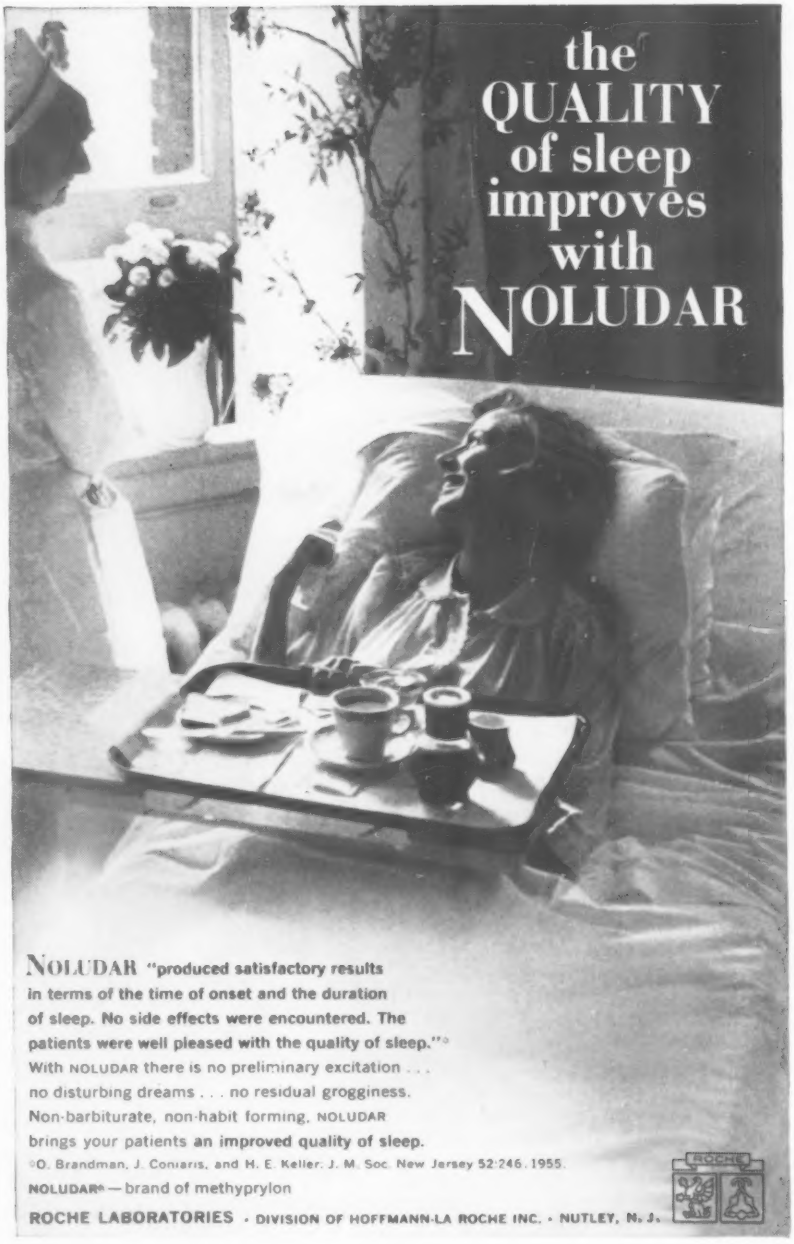


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[1]O. Brandman, J. Coniaris, and H. E. Keller: J. M. Soc. New Jersey 52:246. 1955.

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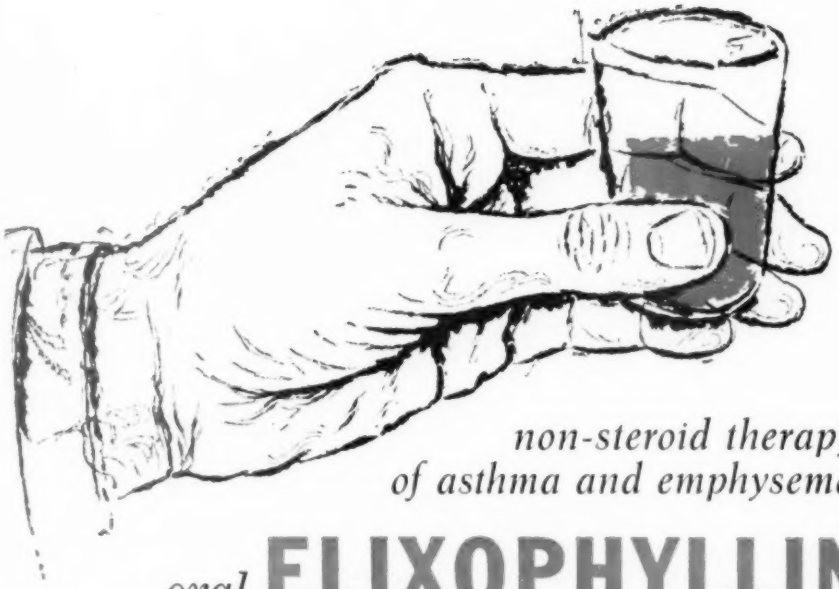

*non-steroid therapy*
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# *oral* ELIXOPHYLLIN

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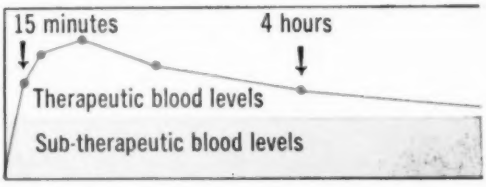
After absorption, theophylline is slowly eliminated. Therapeutic blood levels *endure for hours.**

This predictability of blood levels permits quite constant *therapeutic blood levels night and day,* providing relief of wheezing, dyspnea, cough, and protection against acute attacks for most patients.*

DOSAGE: *First two days:*
45 cc. *(three tbsp.)* on arising;
45 cc. *(three tbsp.)* on retiring;
45 cc. *(three tbsp.)* once midway between above doses *(about 3 P. M.)*




*After two days* of therapy the size of doses should be slightly decreased.
*Each tablespoonful contains:* theophylline 80 mg., alcohol 3 cc.
*Prescription only – bottles of 16 fl. oz.*

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- in pregnancy when vomiting is persistent
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Squibb Trifluprομazine

- provides prompt, potent, and long-lasting control
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- effective in cases refractory to other potent antiemetic agents
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Dosage range 2-10 mg.
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Dosage range 5-15 mg.
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SUPPLY:
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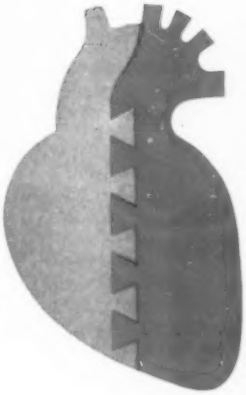

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**Usual dosage:** 1 or 2 tablets q.i.d. *before meals* and at bedtime.
**Dosage should be individualized.** *For clinical supply and literature, write Dept. 25F*

1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:395, *March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, *Dec. 1957.*

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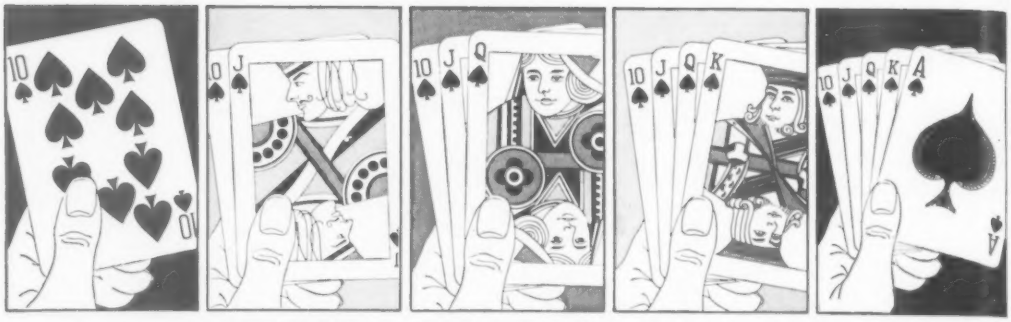

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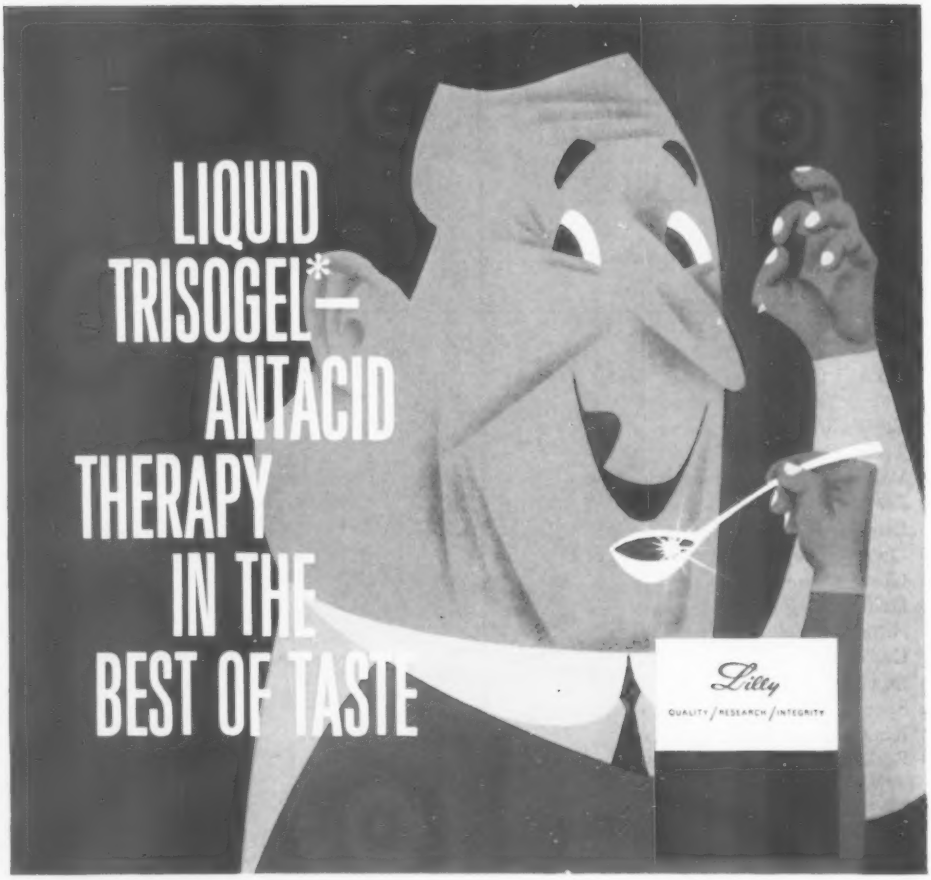


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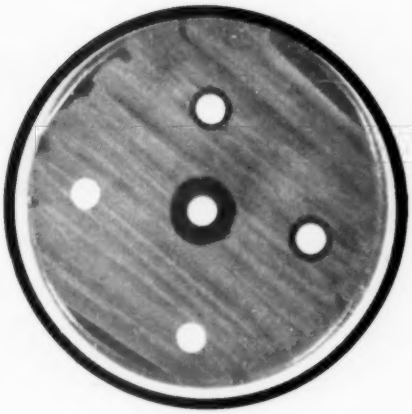
*on the problem of antibiotic-resistant bacteria*



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*Clinical Instructor in Surgery, Stanford University School of Medicine; Clinical Instructor in Surgery (Oncology), University of California School of Medicine; Assistant Chief of Surgery, Mount Zion Hospital, San Francisco, California*

TO internists, general practitioners and surgeons alike, it is apparent that tumors of the breast occur frequently enough to occupy a significant place in the daily practice of medicine. This book presents a complete classification of breast tumors, both benign and malignant. At the same time, Dr. Pollack and his seven contributors give sound, clinically approved guidance on all phases of diagnosis and treatment.

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A chapter on the technique of radiotherapy of breast cancer includes special attention to physical and biological considerations, and to regional spread. This is in addition to a discussion of postoperative *x*-ray therapy presented in an earlier chapter. Along with the many other features of this practical book, internists will find helpful the discussion of oral and parenteral administration of hormones. Endocrinologists will appreciate the detailed management of the adrenalectomized and hypophysectomized patient as well as the general considerations of diagnosis and treatment of breast tumors.

*CONTRIBUTORS*

DONALD E. BERNSTEIN, M.D.
*Adrenalectomy*

GERSON R. BISKIND, M.D.
*Pathologic Classification of Breast Tumors. Medical Treatment of Chronic Cystic Mastitis*

FRANCIS S. GREENSPAN, M.D.
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By

HENRY L. JAFFE, M.D.

*Director of Laboratories and Pathologist, Hospital for Joint Diseases, New York, N.Y.; Consultant, Armed Forces Institute of Pathology, Washington, D.C.*

PRIMARY tumors and various other tumorous conditions affecting the bones and joints are considered fully in this informative, practical book. In addition to individual primary tumors, the book considers tumors metastatic to the skeleton, tumors developing in bones, at sites of damage from noxious agents, and tumors invading bone from overlying soft parts. These conditions are discussed in regard to their clinical features, their roentgenographic aspects and their pathologic manifestations, both gross and microscopic. From these points of view, problems of differential diagnosis are stressed and the broad outlines of treatment are indicated.

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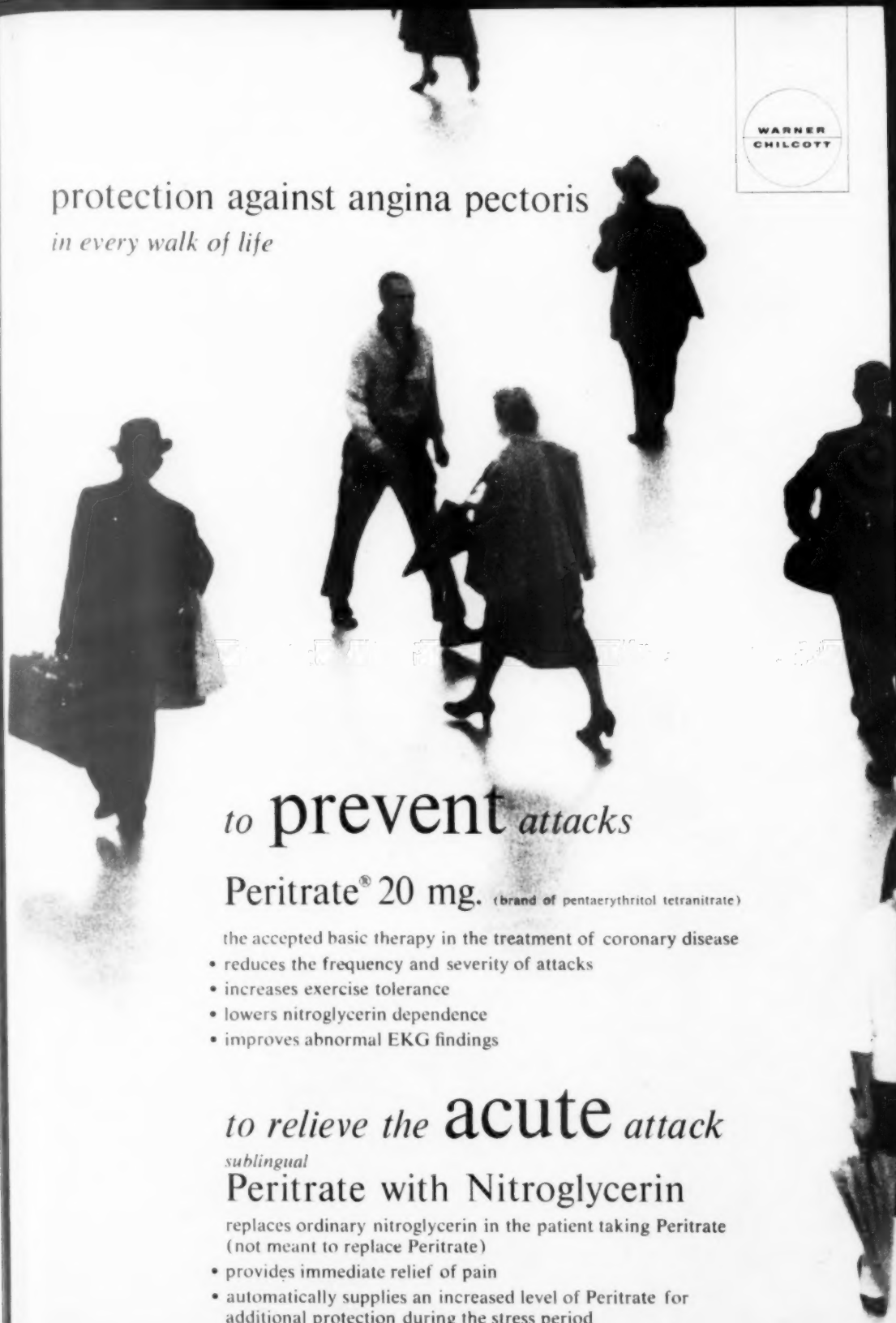


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